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No 1

DIGITALIS DOSAGE *

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NEW YORK

In the course of this investigation I have been struck by the small amount of accurate knowledge that we possess as to practical therapeutics. My experience has been almost exclusively in the laboratory and perhaps I have expected too high a standard in the clinic, but in this field of cardiac tonics alone I see an endless vista of questions to be solved in the clinic if only accurate observations are available. But we have enough of inaccurate therapeutics already, what is needed is not statistical compilation, but an accurate study of each individual case and a careful and, if you will, an experimental investigation of each feature presented¹.

There are probably no more valuable therapeutic agents in our materia medica than digitalis and its several allies and, although digitalis has been in wide clinical use since Withering first brought it to medical attention, in 1785, the important question of its dosage is still in a state of considerable confusion. Clinicians have recommended doses which range from 2 minims of the tincture (less than $\frac{1}{4}$ grain of the leaf) three times daily to 30 minims of the tincture (3 grains of the leaf) three times a day. Although the larger dose in this instance is more than twelve times the smaller, this divergence pales into insignificance when compared with that encountered in the case of strophanthus or strophanthin, which Hatcher and Bailey² reported from the literature. They found that the largest daily dose used was some 750 times as great in terms of activity as the smallest single dose advised by recognized authorities.

In addition to the gross differences everywhere encountered in the stated doses of the galenical preparations of any of the several members of this group of drugs, the universal practice of expressing the dose in the terms of a measured amount of one or another galenical

* Submitted for publication March 16, 1915

* From the Department of Pharmacology of the Cornell University Medical School, New York

1 Cushny, Arthur R. The Therapeutics of Digitalis and Its Allies, The Harvey Lectures, 1910-1911, p 46

2 Hatcher, Robert A., and Bailey, Harold C. Tincture of Strophanthus and Strophanthin, Jour Am Med Assn, 1909, lii, 5

preparation fails to take cognizance of the differences in activity of the preparations themselves. That these differences alone are of no small matter is obvious from the reports of many who have tested these preparations. Edmunds and Hale,³ for example, report variations in the activity of digitalis amounting to 400 per cent, and we have several samples of high grade digitalis leaf in the laboratory, some of which are more than twice as active as others.

The questions of the absorption and excretion, or elimination of the several members of this group and of their preparations have been given little consideration in so far as they enter into the determination of the doses to be used and the frequency of their repetition. The matter of absorption alone is of the utmost importance when the drug is administered orally, and the neglect of this factor has led to much misconception even in the statements of careful and competent investigators. Thus, Cushny⁴ and Turnbull⁵ both call attention to the fact that the tincture of strophanthus, given orally to man, must be used in larger doses than are given of the tincture of digitalis. Cushny says, "The tinctures of strophanthus and squills were weaker in their action on patients than that of digitalis, nearly twice as much being required to elicit changes in the heart." And Turnbull, "Although the tincture of strophanthus employed was twenty times as powerful as the digitalis when tested on the frog's heart the dose necessary to produce effects was usually larger."

These statements give the impression that so far as the effect on the human heart is concerned strophanthus is actually less active than digitalis, when each is given by the mouth. That such is not invariably the case, however, is apparent from the fact that in some instances much less is required of the tincture of strophanthus than of digitalis to produce similar effects. That the true explanation of this apparent difference in the activity of the tinctures of strophanthus and of digitalis is referable to the great variability of the absorption of the former from the alimentary canal has been shown for man by Bailey⁶ and Hatcher and Bailey,⁷ and for the cat by Hatcher.⁸

3 Edmunds, Charles W, and Hale, Worth. The Physiological Standardization of Digitalis, Bull Hyg Lab, 1908, No 48

4 Cushny, Arthur R. Discussion on the Treatment of Non-Valvular Cardiac Disease, Brit Med Jour, 1912, ii, 685

5 Turnbull, H H. The Therapeutic Use of Digitalis, Brit Med Jour, 1910, ii, 1608

6 Bailey, Harold C. A Clinical Study of Crystalline Strophanthin, Jour Pharm and Exper Therap, 1909-1910, i, 349

7 Hatcher, Robert A, and Bailey, Harold C. The Clinical Use of Strophanthus, Jour Am Med Assn, 1910, iv, 1697

8 Hatcher, Robert A. Variation of Dosage Dependent on the Method of Administration, Jour Am Med Assn, 1910, iv, 746

Hatcher and Bailey⁷ reported the case of a patient who took 60 minims of tincture of strophanthus (112 cat units) in two days without showing evidence of cardiac action, and who then suddenly developed very threatening toxic symptoms after the seventh dose of 10 minims, or a total of 130 cat units. Hatcher showed that as much as six times the fatal vein dose of ouabain given orally to cats often failed to kill, and when he subsequently tested the animals was able to prove that not even the smallest quantities of the drug had been absorbed in some instances. On the other hand, when as little as twice the minimal fatal vein dose was given orally to a cat a full fatal dose was absorbed in slightly over two and a half hours in one instance.

To complicate the question of the absorption of the digitalis bodies from the alimentary canal of man—and hence to complicate that of dose—we have often to deal with cases of cardiac failure in which the dilatation of the heart has resulted in splanchnic congestion and vomiting when the patients come under treatment.

It is desirable to know whether the diseased heart responds to digitalis quantitatively the same as the normal organ, and whether or not one type of cardiac disease or disorder responds to a smaller dose than another. The influence of age and sex, if any, should be determined, although they are probably of less importance than the several other factors already mentioned.

The last and an important problem is to determine whether or not there is any method of assaying or standardizing the commonly used preparations of the digitalis group of drugs which will yield results that may be transferable to man.

With this brief glance at the more important problems demanding solution before we may be in a position to say that we really know anything about the question of the dosage of digitalis, other than in a general way I will proceed to the presentation of the details of a series of observations bearing on some of these problems which I have been pursuing for the past two years.

PLAN AND SCOPE OF OBSERVATIONS

Inasmuch as the usual method of administering digitalis is by mouth it was thought best to restrict the observations to this mode of giving the drug. The general problem for investigation was to determine whether or not it was possible to establish the dose of digitalis for man on the basis of its activity. With this there were associated several other problems directly concerned in the question of the dosage of this drug and its allies and pure principles. These may be recapitulated as follows:

- 1 The rate, degree and uniformity of the absorption of the crude drug and its active principles
- 2 The influence of sex, age, and weight on the dose
- 3 The influence of the preparation—infusion, tincture, etc—on the dose
- 4 The influence of the cardiac condition
- 5 The influence of the size of the daily dose on the total dose required

For the investigation the following preparations were used (a) tinctures made in the laboratory from digitalis leaves from different sources and varying in activity, (b) infusions from different leaves and of different activities, (c) crystalline digitoxin in solution in 70 per cent alcohol, or made into tablet triturates with milk sugar, (d) true digitalin of Kiliani, and digitalin

All of these preparations were standardized biologically by the cat method of Hatcher⁹ and the activity of each was determined in terms of the cat unit¹⁰

The most active tincture used was 23 times as potent as the weakest as shown by this method of standardization. The most active infusion was 216 times as strong as the weakest, although the infusions were not always prepared from the same leaves as the tinctures.

The same specimen of crystalline digitoxin was used throughout the observations, its activity, therefore, being uniform. However, both the solutions and the tablet triturates were tested after being made, to ascertain their activity.

When the infusions were used they were prepared fresh on the day of the beginning of treatment in each case, and standardized at once. During the time any of the infusions was being given, which never exceeded two days, the preparation was kept tightly stoppered and in the ice box to prevent possible deterioration. Recent experiments have shown us that this precaution was probably unnecessary, as with ordinary care of preparation the infusion should keep for several days at room temperature without material loss of activity.

Owing to certain inherent difficulties in their use the tests of both true digitalin and digitalin were early abandoned, but mention of the former will be made subsequently. The tincture of strophanthus was not used in these observations because of the great variability of

9 Hatcher, Robert A., and Brody, J. G. The Biological Standardization of Drugs, *Am Jour Pharm*, 1910, lxxxii, 360

10 The cat unit may be defined as that amount of the drug which is just sufficient to kill one kilogram of cat when slowly and continuously injected into the vein. This is expressed in terms of milligrams of the drug, whether it be a pure principle or the leaf.

its absorption from the alimentary canal of man. This fact has already been discussed, and I might here add that, on account of this variability and of its great activity when it is absorbed, I regard its oral administration to man to be so dangerous as to make its use in this way wholly unwarrantable. The same can be said with equal truth of ouabain (crystalline strophanthin of Thoms), the official amorphous strophanthin, and of convallaria. The several other members of the digitalis group of drugs were omitted from consideration because they possess no advantages over digitalis itself, or because they are too infrequently used clinically to warrant their inclusion.

The cases on which the studies were made were unselected so far as their cardiac or general conditions were concerned and included both those in which there was auricular fibrillation and those in which the normal pacemaker was in control of the heart. A few cases were also included in which the heart was not primarily at fault. Two considerations did act to cause some selection, however. The first was that the patient had to be one to whom the drug could be given orally and, with a few exceptions, this excluded patients who were in extremis on admission and who required the immediate injection of ouabain or strophanthin. The second, and the more important consideration for this study, was that it be definitely ascertained that the patient had not received any one of the digitalis group of drugs within a period of not less than three weeks prior to the beginning of observation. It is scarcely necessary to state that no exception was made to this rule.

In every case in which it was possible, without jeopardizing his welfare, the patient was kept in bed without medication other than a possible cathartic or mild hypnotic for a period of from three to seven days before the digitalis or digitoxin was given. During this interval he was weighed at least once, and was given a diet which could be continued without material alteration throughout the course of active treatment. In edematous cases the daily intake of fluids was restricted to a measured amount—usually 40 ounces—and the total amount of urine voided in each twenty-four hours was accurately measured and recorded. In some cases the systolic and diastolic blood pressures were taken daily at the same hour and by the same observer. Such other observations as were demanded in any given case were made and recorded in order to make the conclusions as to the progress of the case under the influence of the drug the more accurate.

During the preliminary period of observation, throughout the time of the administration of the drug, and for a variable period of time after its discontinuance, frequent clinical examinations were made and their results at once committed to writing to reduce error to a mini-

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In addition to the information to be gained by careful clinical
vation, frequent polygraphic tracings were taken and in some
electrocardiographic records were also secured

was hoped by taking all of these precautions that the element
y personal judgment as to the effects of treatment and the times
eir inception might be reduced to a minimum It must be under-
, however, that in the estimation of the progress of any case of
ac disease the personal element of the observer is bound to
a large and important part, for it is often necessary to interpret

TABLE 1—CASES SHOWING—

Weight in Lbs	Age	Preparation No	Earliest Evidences of Action	Dose in c c	Dose in Cat Unit per Lb
193	60	Tr Dig 65*	Diuresis, clin impr †	15	0 119
160	40	Tr Dig 65			
150	42	Tr Dig 65	Clin impr	14 65	0 150
156	62	Tr Dig 90	Clin impr	12	0 085
140	45	Tr Dig 105			
136	69	Tr Dig 148	Slight clin impr	10	0 049
138	59	Tr Dig 150	Slight clin impr	8	0 039
127	49	Tr Dig 150	Marked clin impr	19	0 100
103	48	Tr Dig 150	Marked clin impr	15	0 097
107	58	Inf Dig 163			
130*	55	Inf Dig 180	Clin impr	150	0 096
110	68	Inf Dig 120			
148	43	Digitoxin‡	Marked clin impr	Mg 1 5	0 029
112	68	Digitoxin	Marked clin impr	2 5	0 0637
117	75	Digitoxin (tab)	Marked clin impr	2 5	0 061

* The number of the tincture or infusion of digitalis is the same as the number of milligrams of

† The abbreviation clin impr denotes clinical improvement as defined in the text H B indicates

‡ In the case of digitoxin the cat unit is constant and is 0 35 mg per kilogram

changes observed in the light of previous conditions or of
aneous modifying factors The independent opinions of the mem-
s of the house and visiting staffs of the hospitals in which the
ork was conducted were solicited, and in a number of cases the
cision as to the effect of treatment was reached after a discussion
which several of us took part

ILLUSTRATIVE CASES

In order to make the method of the study of the cases clearer,
stracts of the essential features in the records of four cases illus-

trating somewhat different conditions and results of treatment are presented

Patient J C—(Case 14 in Table 1), a man aged 68, was admitted to the hospital at about 3 p m, Oct 6, 1914, with the diagnosis of chronic cardiac valvular and myocardial diseases and auricular fibrillation. There was no history of antecedent rheumatism. When admitted he was complaining of precordial pain, swelling of his feet and legs, and shortness of breath. His condition was regarded as serious and urgent. The pulse was scarcely palpable at the wrist, very rapid, and extremely irregular in both force and rhythm. Cyanosis was marked and dyspnea and orthopnea extreme. Polygraphic tracings were unsatisfactory, but confirmed the presence of auricular fibrillation.

—AURICULAR FIBRILLATION

Full Therapeutic or Minor Toxic Action	Dose in c c	Cat Units per Lb	Total Dose in c c	Cat Units per Lb	Duration of Treatment	Remarks
Nausea, H-B	25	0 198	30	0 238	4½ days	No emesis from total
Nausea, C R, H-B	13 3	0 127			16 hrs	No emesis from total
Vom, H-B	16	0 164	17 5	0 179	2¾ days	
H-B	16	0 113	31	0 220	4 days	No emesis from total
H-B	16	0 108			36 hrs	No nausea
H-B	26	0 128	32	0 184	4 days	No nausea
H-B	30	0 144			4½ days	No nausea
H-B	24	0 125			1 day	No nausea
Nausea, H-B	35	0 226			4½ days	
H-B	120	0 103	135	0 115	22 hrs	Vom from total
H-B	160	0 102			1 day	No nausea
H-B	200	0 227	240	0 272	1½ days	No nausea
H-B	Mg 2 5	0 048			3 days	No nausea
Vom, H B	3 0	0 076			18 hrs	
Vom, H-B	3 5	0 085			1 day	

the leaf in each cat unit
heart block, which was partial in all cases C R stands for coupled rhythm

It was necessary to begin treatment promptly, and Table 2 gives the chronologic course of events in treatment and progress.

At 10 a m, Oct 7, after he had received a total of 25 mg of digitoxin in the twelve-hour period from 6 p m the evening before to the corresponding hour on the morning of the seventh, his dyspnea was less marked, orthopnea decidedly lessened, and the pulse slower, fuller, and of much better force. The cyanosis had been greatly reduced and the general condition of the patient was very decidedly improved over that of the evening before. On the morning of the eighth scarcely any dyspnea, orthopnea or cyanosis remained, the patient could lie almost flat without respiratory distress, and it was obvious that the full therapeutic effect of the digitoxin had been secured. Tracings taken shortly before the appearance of vomiting showed marked slowing, which was due to the production of a partial heart-block.

Patient P A—(Case 5 in Table 2), a man aged 26, was admitted to the hospital June 8, 1914, with the diagnosis of cardiac valvular disease, mitral insufficiency and aortic stenosis. There was a history of previous attacks of rheumatism, the Wassermann reaction was negative. When admitted he was complaining of precordial pain, cough and shortness of breath. Rest in bed with a restricted diet for a week from the time of admission (to June 15) produced little or no change in his condition, and failed to slow his heart. Polygraphic tracings taken at 2 p m on the fifteenth showed the rate to be about 92 per minute with the rhythm normal. At midnight, June 15, he was given 80 cc of tincture of digitalis No 97 at a single dose. Ten hours later (10 a m on the sixteenth) tracings showed the pulse rate to be only 81 per minute, a drop of 11 beats, and the rhythm was then distinctly coupled. The patient said that he was much more comfortable. During the day of the sixteenth the precordial pain and dyspnea almost disappeared. The cough rapidly subsided and although no further digitalis was given, the patient made a rapid recovery and was discharged June 27.

TABLE 2—CHRONOLOGIC COURSE OF EVENTS IN TREATMENT OF J C

Date 1914	Hour	Digitalis, Mg	Heart Rate	Radial Pulse	Defect	Total Urine in 24 Hrs	Remarks
10/ 6	4 p m		170	135	35		
	6 p m	15					
	12 p m	05					
10/ 7	6 a m	05				18 ounces	14 hours only
	10 a m		94	88	6		Marked improvement
	12 m	05					
	12 45 p m						Vomited, heart block
	3 30 p m		91	83	8		
10/ 8	10 a m		94	85	9	53 ounces	
	4 30 p m		92	88	4		
10/ 9	9 a m		86	82	4	41 ounces	
10/10	9 30 a m		82	75	7	73 ounces	

Patient B B—(Case 33 in Table 3), a woman aged 49, was admitted to the hospital Oct 20, 1914, with the diagnosis of chronic cardiac myocardial and valvular diseases, mitral insufficiency, hepatic cirrhosis. When admitted she was complaining of swelling of abdomen, shortness of breath, and cardiac palpitation. Her pulse was rapid and of poor force but regular in rhythm, there was considerable edema and ascites, and the respiration was rapid and embarrassed. Free catharsis, diet with fluid intake restricted to 40 ounces in the twenty-four hours, and rest in bed were without beneficial effect, although continued for five days. Tablet triturates, each containing 05 mg of digitoxin, were given from November 4 to 6 as follows: November 4 at 6 p m two tablets (10 mg), one tablet at midnight (05 mg), November 5 one tablet every six hours to and including the 6 a m dose on November 6. The total taken was 40 mg in a period of thirty-six hours.

A note made at 11 30 a m, November 5, states "No demonstrable evidence of digitoxin action after 20 mg in twelve hours." And a note made at 10 the following morning states "Very slight sinus arrhythmia this morning. No other signs of digitalis action on the heart except stronger and fuller pulse. Has had total of 40 mg of digitoxin. Complains of slight nausea which was

first noticed yesterday afternoon after a total of 25 mg digitoxin had been taken" Although the patient vomited twice on the afternoon of November 5 there was still no influence of the digitoxin on the rate of her heart and the drug produced no beneficial action •

Patient F C—(Case 34 in Table 3), a man aged 37, was admitted to the hospital Nov 13, 1914, complaining of swelling of scrotum and legs, weakness on exertion, dyspnea, orthopnea, and cardiac palpitation Diagnosis Chronic parenchymatous nephritis, pericarditis with effusion, cardiac hypertrophy and dilatation, mitral insufficiency

Tablet triturates, each containing 0.5 mg of digitoxin, were given as follows November 17, two at 6 p m and again at midnight, November 18 at 6 a m, one tablet, and this dose was then ordered to be repeated every six hours night and day and its administration thus continued until the 6 a m dose was given on November 20, making a total of 65 mg in sixty hours

The following indications of the progress of this case are taken from notes made at the time

November 17, 9 30 a m No improvement in the patient's condition has resulted from rest and the restriction of the intake of fluid to not over 40 ounces in twenty-four hours The edema is still very marked, the pulse continues rapid, and dyspnea and orthopnea still trouble him Polygraphic tracings show regular rhythm, disturbed only by a slight grade of sinus arrhythmia which is for the most part synchronous with respiration

November 18, 10 a m Pulse rate and rhythm continue unchanged since yesterday, but the dyspnea is decidedly less and the urinary output has increased This after 25 mg of digitoxin in twelve hours

November 19, 9 30 a m Clinical improvement is very marked, the pulse and respiration rates range somewhat lower, both the dyspnea and orthopnea are much diminished and diuresis is marked There is no nausea The patient has now taken 45 mg of digitoxin in thirty-six hours and the full therapeutic effects of the drug are becoming manifest

November 20, 10 a m Patient nauseated early last night and he has vomited twice The vomiting came on after 55 mg of digitoxin had been taken, but the administration was continued to the 6 a m dose, making a total of 65 mg in sixty hours Diuresis very marked, edema nearly gone, respiration slower, no orthopnea Pulse slowed through partial heart-block, the fourth or fifth ventricular beat being regularly blocked The observations recorded in the course of treatment of this patient are graphically presented in the accompanying chart¹¹

In the presentation here given of these four cases all but the essential features have been omitted for the sake of brevity All other points were observed which contributed to the formation of a conclusion as to the exact status of the individual patient at the time of each examination

A total of fifty-three courses of treatment were followed in this study and comprise the material shortly to be subjected to analysis These fifty-three courses were carried out on forty-seven patients, there being six instances in which one patient either remained in the hospital long enough to require a second or third course, or returned

¹¹ The very large dose of 65 mg of digitoxin given to this patient was administered under exceptional conditions and, though the patient made a satisfactory and complete recovery without untoward incident, such a large dose is distinctly not advised

TABLE 3—

No	Weight in Lbs	Age	Preparation No	Earliest Evidence of Action	Dose in cc	Dose in Cat Unit per Lb
1	17	27	Tr Dig. 97	Clin Impr. S A	12	0.145
2	10	52	Tr Dig. 97			
3	174	28	Tr. Dig. 97	Slight clin impr	12	0.091
4	129	60	Tr Dig. 97	Diuresis, clin impr	10	0.050
5	121	29	Tr Dig. 97			
6	178	42	Tr Dig. 97	Diuresis, clin impr, S A	8	0.032
7	120	67	Tr Dig. 97	Diuresis, clin impr, S A	8	0.093
8	144	60	Tr Dig. 97	Clin impr, S A	16	0.114
9	144	60	Tr Dig. 97	Clin impr S A	16	0.114
10	148	74	Tr Dig. 97	Clin impr	6	0.041
11	141	40	Tr Dig. 97	Marked clin impr	16	0.116
12	172	64	Tr Dig. 97	Clin impr, S A, ex syst	12	0.092
13	172	56	Tr Dig. 97	Clin impr, S A, diuresis	17	0.101
14	129	54	Tr Dig. 105			
15	145	54	Tr Dig. 120	Marked clin impr	17	0.091
16	140	48	Tr Dig. 148	Clin impr	25	0.120
17	160	48	Tr Dig. 150	Clin impr, slowing	20	0.133
18	52	11	Inf Dig. 83			
19	131	61	Inf Dig. 110			
20	145	60	Inf Dig. 110	Clin impr, S A	100	0.093
21	52	8	Inf Dig. 120			
22	145	32	Inf Dig. 180	Clin impr, diuresis, S A	125 Mg	0.072
23	133	45	Digitoxin	Slight clin impr, S A	15	0.032
24	123	15	Digitoxin	Clin impr, slowing	20	0.045
25	131	60	Digitoxin			
26	131	60	Digitoxin	Clin impr, slowing	125	0.027
27	165	59	Digitoxin	Clin impr, diuresis	15	0.026
28	154	40	Digitoxin	No clin impr, ex syst	30	0.055
29	113	39	Digitoxin	Clin impr, S A	125	0.0315
30	113	39	Digitoxin	Clin impr, S A	125	0.0315
31	151	46	Digitoxin	Clin impr, S A, H B	25	0.047
32	145	52	Digitoxin	No clin impr, S A	175	0.034
33	130	49	Digitoxin (tab)			
34	162	37	Digitoxin (tab)	Clin impr, diuresis	25	0.044
35	145	60	True digitalin	Clin impr, slowing	80	0.036
36	142	34	True digitalin	Slight S A only	160	0.075
37	93	38	Digitalein			
38	93	38	Digitalein	Slowing only	480	0.147

* In this table the number of the digitals is the same as the number of milligrams in one cat unit
 † Clin impr denotes clinical improvement as defined in text H B indicates heart block, which was
 ‡ The cat unit of digitoxin is 0.35 mg per kilogram
 § The cat unit of true digitalin is 1.5 mg per kilogram
 ¶ The cat unit of digitalein is 3.5 mg per kilogram

—NONFIBRILLATING CASES

Full Therapeutic or Minor Toxic Action	Dose in c c	Cat Unit per Lb	Total Dose in c c	Cat Unit per Lb	Duration of Treatment	Remarks
Clin ev, S A	14	0 169			1 day	No nausea
Vom, slight clin impr	47	0 293	59	0 368	5 days	
Vom, slight clin impr	24	0 182			1¾ days	Pulmonary tuberculosis
Clin ev, diuresis	16	0 127	44	0 350	6 days	Vom from total
Clin ev, slowing, C R	8	0 068				Single dose
Diuresis, slowing, S A	24	0 150			3 days	First effect after single dose
Diuresis, slowing	10	0 086			18 hrs	First effect after single dose
Clin ev, slowing, S A	32	0 228			4 days	No nausea
Clin ev, slowing, S A	18	0 123			3 days	Same case as No 8
Clin ev, slowing	12	0 082			30 hrs	First effect after single dose
Nausea, clin ev	26	0 190	28	0 200	3½ days	No vom
H-B, clin ev	18	0 133	26	0 200	60 hrs	No vom
S A, clin ev	29	0 174			2½ days	No nausea
S A, clin ev	7	0 051				Single dose
Nausea, diuresis, S A	25	0 133			36 hrs	
Clin ev, H-B	35	0 168	45	0 217	3 days	Naus after 39 c c = 0 18 c u per lb
Mod clin impr	66	0 440			5 days	No toxic symptoms
S A	30	0 104			28 hrs	No clin impr
Vom, no clin impr	140	0 145	180	0 187	36 hrs	Vom only once
Naus, clin ev, S A	200	0 186			42 hrs	
Naus, no clin impr	55	0 130			12 hrs	
Clin ev, S A, slowing	230	0 132			2 days	No nausea
Clin ev, S A, slowing	Mg 3 625	0 077			5½ days	No nausea
Nausea, clin ev	4 75	0 110	5 5	0 127	7 days	Vom after total
Nausea, H-B, ex syst	1 75	0 038			1½ days	Same case as No 19
H-B, ex syst	2 25	0 049			2 days	Same case as No 19
Naus, diuresis, slowing	3 50	0 060			64 hrs	No vomiting
No clin impr, ex syst	3 00	0 055	4 0	0 073	3½ days	No nausea
Clin ev, S A	2 50	0 063	3 5	0 088	2½ days	Naus after total
Clin ev, S A	2 50	0 063			1½ days	No nausea Same as No 29
Vom, clin ev, H-B	3 50	0 066			1½ days	
Naus, clin ev, S A	3 50	0 068			2 days	
Naus, no clin impr	2 50	0 054	4 0	0 087	1½ days	Vom after total
Diuresis, S A, slowing	4 50	0 079	6 5	0 114	60 hrs	Vom after 5 5 mg = 0 096 c u per lb
Clin ev, S A	28 0	0 128			3 days	No nausea Same as No 20
Diuresis, slight S A	180 0	0 840			4¼ days	No nausea
Slowing, ex syst	36 0	0 110			44 hrs	No nausea
Slowing, ex syst	64 0	0 196			3 days	Same case as No 37

partial in all cases S A stands for sinus arrhythmia C R stands for coupled rhythm Clin ev

to the hospital within a few months after discharge. For the sake of brevity and to obviate the necessity of the reader's having to search through the abstracts of case histories, the essential features of each case, so far as the present problems are concerned at least, are presented in Tables 1 and 3. In this form the observations lend themselves more readily to analysis, and it is from these tables that most of my later figures will be drawn. In these tables it has been impos-

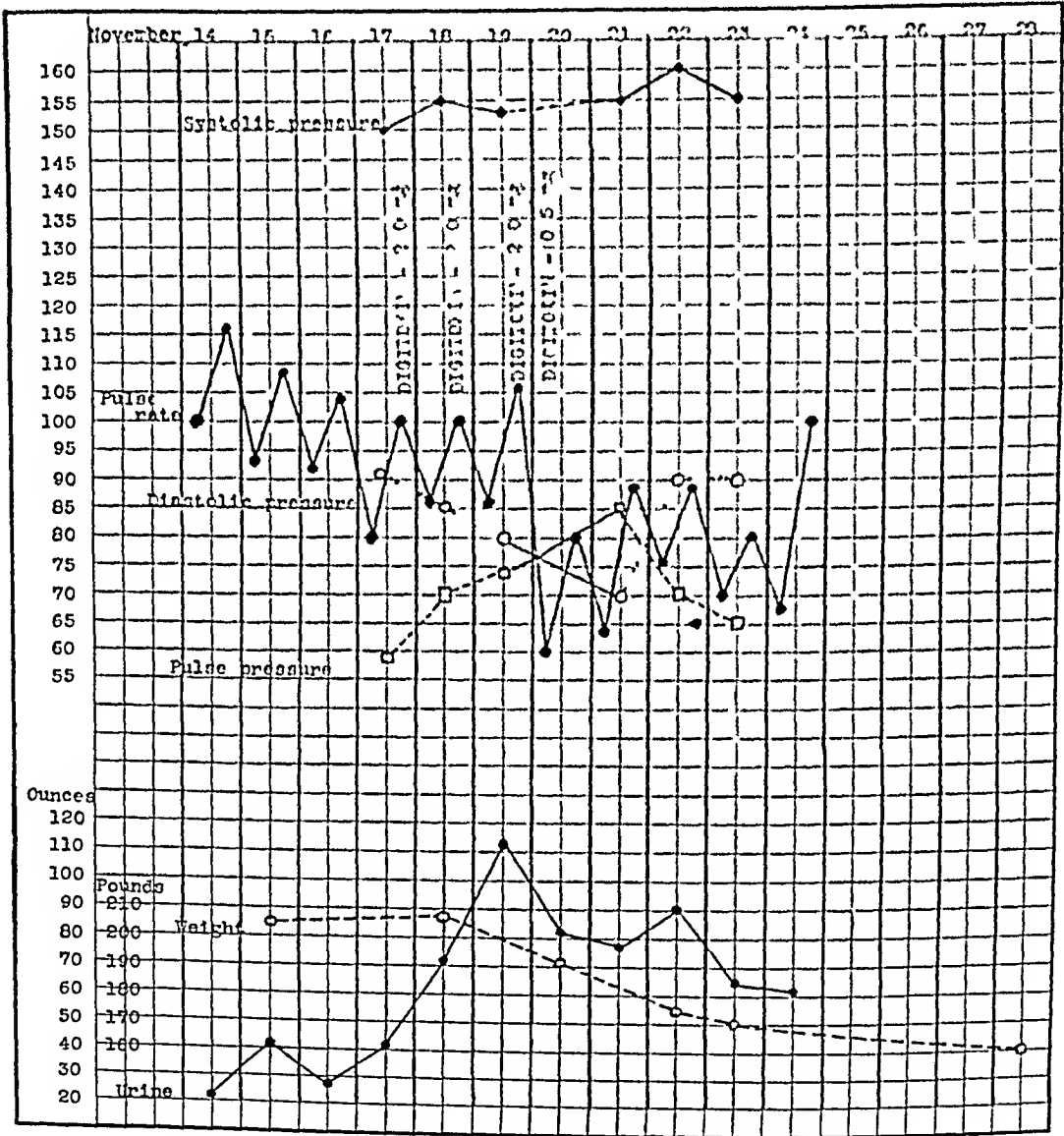


Chart showing course of events in treatment of Patient F. C.

sible to do more than to indicate the type of phenomena present at any of the stages of action recorded, and the significance of some of the terms employed needs definition.

CLINICAL IMPROVEMENT

Exception may be taken to the use of a term apparently so loose as this in a paper in which an effort is to be made to arrive at

numerical results The term is here employed to express the sum total of all of the factors which go to make up the purely clinical features indicative of improvement, exclusive of all traceable cardiac phenomena Such clinical features differ in type with the different cases and they include both subjective and objective phenomena Among the former some of the most trustworthy are the patient's voluntary statements as to improvement in his respiration, the ability to lie flatter in bed without suffering respiratory oppression, disappearance of the sensation of epigastric fulness, distress, or pain, disappearance of nausea or vomiting due to congestion, loss of precordial and referred pains; and the disappearance of cardiac palpitation

The more usual objective symptoms of value are a fall in the pulse and respiration rates, the more or less rapid subsidence of dyspnea and orthopnea; disappearance of persistent cough, and the clearing up of the signs of congestion at the lung bases The gradual decrease in the pulse deficit in cases of auricular fibrillation, more or less rapid disappearance of the signs of a congested liver and splanchnic region such as, loss of tenderness over the enlarged liver or the epigastrium, diminution in the size of the liver, disappearance of its pulsation, and the vanishing of tympanites are all signs of first importance So also are the clearing up of cyanosis and cold extremities, the disappearance of edema, and an increase in the urinary output

Such symptoms as these, in varying combinations, go to make up the picture denoted "clinical improvement," and in some cases in which one symptom stood out most prominently it has been indicated in the table So, also, the clinical improvement has been indicated according to degree as slight, moderate, or marked

The classification which includes all such phenomena as marked sinus arrhythmia, partial heart-block, extra systoles, etc., as minor toxic effects of digitalis, has been adopted in this discussion In addition to these both nausea and vomiting have been included as minor toxic symptoms because they appear so frequently in close association with one or another of the previously mentioned phenomena Further all of these strictly *minor* toxic phenomena appear, in cases amenable to benefit by digitalis, so nearly simultaneously with the development of the fullest obtainable therapeutic effects that these two sets of phenomena have been grouped under the same rubric, although there will be occasion to separate them for subsequent analysis

All of this attention has been devoted to the presentation and elucidation of the plan and scope of these observations in order to enable the reader to follow the ensuing discussion of the results the more easily, and to place him in a position to analyze the findings for himself in any way he may desire I might say that I arrived at just

this point in the actual conduct of my work on the problems in hand without any very definite idea of what the observations would show, for I made no analysis of them until the work of observation was completed. In this way I hoped to avoid the pitfall of the preconceived idea

ANALYSIS OF OBSERVATIONS

As previously stated, the material for such analyses as will now be undertaken is set forth in Tables 1 and 3. It will be seen that each table gives the weight of the patient in pounds, the age of the patient, the preparation of digitalis which was used, together with its activity in terms of the cat unit, the actual amount of the preparation required to produce the several types of effects recorded, the amount of each preparation similarly required calculated on the basis of activity in fractions of a cat unit per pound of the body weight of the patient, and finally, the total period of time during which the drug was administered, with certain remarks on individual cases which were deemed of value for their better understanding. With these tables available for reference we may proceed at once to the discussion of certain of the phases of the question in hand.

AVERAGE DOSES WITH MAXIMUM VARIATIONS FROM AVERAGE, IN FRACTIONS OF A CAT UNIT OF ACTIVITY PER POUND OF BODY WEIGHT OF PATIENT

These doses were determined in the following manner. The actual amount of the preparation administered up to the time of production of the effect in question was known, and this was reduced to terms of milligrams of the leaf in the case of the galenical preparations of digitalis. The cat unit of activity for each preparation had been established and, as this is always stated in terms of milligrams of digitalis leaf irrespective of the preparation, the total number of cat units which the patient received could be readily determined by division of the total number of milligrams by the number in each cat unit. The total number of cat units which were taken was then divided by the weight of the patient in pounds and the resulting figure gave the fraction of a cat unit which had been actually taken per pound of body weight to produce the effect in question. With the pure principles the first step was not required, for they were always given in terms of milligrams of the dry substance. The fractions of a cat unit per pound actually taken by each patient are recorded in the tables for each effect produced, and from these figures Tables 4 and 5 have been prepared in which are set forth the average doses for three preparations—tincture and infusion of digitalis, and crystalline digitoxin—for the production of each effect recorded, together with the maximum

and minimum doses which gave similar effects in any case, the range of variation from the average, and the number of cases entering into the computation of the average doses

Table 4 gives the doses in the fifteen cases of auricular fibrillation. A larger number of observations would have been desirable but more patients fulfilling the strict requirements were unfortunately not available. Even with this relatively small number of cases the results are far more uniform than might reasonably have been expected. It must be borne in mind that there is a great difference between determining the fatal dose of a drug for one of the lower animals by intravenous administration or subcutaneous injection and attempting to determine

TABLE 4—AVERAGE DOSES IN FRACTIONS OF A CAT UNIT PER POUND OF BODY WEIGHT, WITH MAXIMUM AND MINIMUM DOSES AND THE PERCENTAGE VARIATIONS, IN CASES WITH AURICULAR FIBRILLATION

Effect Produced	Preparation	No of Cases	Average Dose	Maximum Dose	Percentage Above	Minimum Dose	Percentage Below
Earliest	Tinctures	7	0.091	0.150	64	0.039	58
	Infusions	1	0.096				
	Digitoxin	3	0.051	0.0637	24	0.0289	44
Therap. without naus or vomit	Tinctures	5	0.123	0.144	17	0.108	13
	Infusions	3	0.144	0.227	57	0.102	25
	Digitoxin	1	0.048				
Nausea or vomiting	Tinctures	4	0.179	0.226	26	0.127	30
	Infusions	1	0.115				
	Digitoxin	2	0.080	0.085		0.076	
Therapeutic, all cases	Tinctures	9	0.148	0.226	51	0.108	26
	Infusions	3	0.144	0.227	57	0.102	13
	Digitoxin	3	0.069	0.085	23	0.048	31
Total taken	Tinctures	4	0.205	0.238	16	0.179	13
	Infusions	2	0.193	0.272		0.115	

a dose for man when the drug is given by mouth, in which case the factors of absorption may play an important rôle in modifying the dose. And, further, it must be remembered that in the case of the human subject we have no sharply fixed and constant end-point which can be reached in all cases, but that on the contrary the end-point for each determination of dose must of necessity be somewhat different in any two cases. The determination of just that dose which may be regarded as effective in any given case, must depend on what, in that case, one is compelled to take as the index of effectiveness. The attempt to determine the several doses on man as compared to the determination of the activity of the same preparations on the lower animals presents a certain analogy to the performance of two titrations, in the one case using an indicator with no very sharp color change to mark the end reaction, in the other using one with a very decided and sharp change of color which appears precisely at the

change in reaction. It is no wonder, therefore, that the figures should show some range of variation. Indeed, it seems remarkable that the variation was not very much greater than has actually been found.

From Table 4 we see that the greatest range of variation from the average dose for both the tincture of digitalis and for digitoxin was encountered with that dose which produced the earliest evidences of action. This was to be anticipated under existing conditions. The first effects produced are not necessarily alike in any two cases, even among fibrillating hearts. But more important is the fact that it was my practice to give relatively large initial doses with the earlier repetitions also of quite large size, so that it is more than likely that in a few cases somewhat smaller amounts might have given evidence of some action. But even here the extreme range of variation from the average in seven cases receiving the tincture of digitalis is only 122 per cent of the average dose—64 per cent above in one case, and 58 per cent below in another—but reference to Table 1 will show that the doses taken by four of the seven patients for the production of earliest effects differed very slightly from the average of 0.091 cat unit per pound.

Where nausea or vomiting was taken as the effect for which the dose was to be determined the variation from the average was found to be much less than in the case of the earliest effects. Thus, of four patients developing these symptoms after taking the tincture of digitalis, one required a dose 26 per cent above the average and another developed the symptom with a dose 30 per cent below the average. Only two patients vomited from digitoxin, and the doses producing emesis lay very close together.

Under the caption, "therapeutic, all cases" are included all of the cases recorded in the columns devoted to the full therapeutic or minor toxic actions in Table 1. The average dose of tincture of digitalis required to produce these effects was 0.148 cat unit per pound, and the largest and smallest doses recorded show a variation of 51 per cent above and 26 per cent below the average, or a total range of variation of 77 per cent. The doses determined for three patients receiving infusion of digitalis lay very close to those just stated for the tincture, in average, maximum, and minimum. The total range of variation from the average dose was decidedly less with digitoxin, amounting to only 54 per cent. This narrower range is possibly due in part to the small number of cases receiving digitoxin in this series.

Turning to Table 5, which embodies the corresponding observations made in cases without auricular fibrillation, we find both a larger number of observations and a rather wider range of variation, in isolated cases, from the averages determined. From fourteen courses of

administration of the tincture an average dose of 0.097 cat unit per pound was established for the production of the earliest effects, and the total variation from this average rose to 121 per cent—one case requiring 49 per cent more than the average, and one responding to 72 per cent less. As in the previous series of observations, here too, the range of variation from the average in the case of digitoxin is found to be smaller than in the case of the tincture of digitalis, being only 78 per cent total—48 per cent above and 30 per cent below.

For the production of nausea or vomiting the average doses were determined from six patients who received the tincture, three the infusion, and eight digitoxin. The total range of variation in the

TABLE 5—AVERAGE DOSES IN FRACTIONS OF A CAT UNIT PER POUND OF BODY WEIGHT, WITH MAXIMUM AND MINIMUM DOSES AND THE PERCENTAGE VARIATIONS, IN NONFIBRILLATING CASES

Effect Produced	Preparation	No of Cases	Average Dose	Maximum Dose	Percentage Above	Minimum Dose	Percentage Below
Earliest	Tinctures	14	0.097	0.145	49	0.041	72
	Infusions	2	0.032	0.093		0.072	
	Digitoxin	10	0.037	0.055	48	0.026	30
Therap. without naus or vomit	Tinctures*	12	0.130	0.223	75	0.051	61
	Infusions	2	0.118	0.132		0.104	
	Digitoxin	6	0.064	0.079	23	0.049	24
Nausea or vomiting	Tinctures	6	0.221	0.350	58	0.133	40
	Infusions	3	0.153	0.186	21	0.130	16
	Digitoxin	8	0.072	0.110	52	0.038	48
Therapeutic, all cases	Tinctures†	16	0.148	0.293	97	0.051	66
	Infusions	5	0.139	0.186	33	0.104	26
	Digitoxin	12	0.065	0.110	69	0.038	42
Total taken	Tinctures‡	5	0.267	0.368	37	0.200	26
	Infusions	1	0.187				
	Digitoxin	5	0.096	0.127	32	0.073	23

* Exceptional Case 17 omitted. If included, average becomes 0.154 cat units per pound.

† Exceptional Case 17 omitted. If included, average becomes 0.165 cat units per pound.

‡ Exceptional Case 17 omitted. If included, average becomes 0.295 cat units per pound.

case of the tincture was 98 per cent of the average dose, in that of the infusion 37 per cent (only three cases), and in that of digitoxin 100 per cent.

When the production of the full therapeutic or minor toxic actions is considered the total variation in the case of the tincture rises abruptly, on account of a single case, to 163 per cent, but attention is to be called to the fact that this greater variation is not due so much to the occurrence of instances of greater susceptibility to the effects of digitalis as to those of abnormal tolerance¹². Administration of the

12 I have encountered one instance of very great tolerance to the effects of digitalis in which 0.44 cat unit per pound induced only moderate clinical improvement without any toxic symptoms. Whether or not this was due to defective absorption I am unable to state. I have not included this case in the computation of any of the averages here recorded. The details will be found under No. 17 in Table 3.

THE ARCHIVES OF INTERNAL MEDICINE

sion to the production of full therapeutic effects in five cases gave its in which the variation was relatively slight, the total being 59 per cent. of the average dose. The results obtained from administration of digitoxin to twelve patients to the same point fall an intermediate position between those recorded for the tinctures and infusions. Thus the total variation is here found to be 111 per cent. of the average dose.

Tables 4 and 5 give the complete data along these lines of analysis in all of the cases in each of the two groups, but sufficient illustrations have been drawn from them to indicate the ordinary ranges of

TABLE 6—AVERAGE DOSES IN FRACTIONS OF A CAT UNIT PER POUND OF BODY WEIGHT, WITH MAXIMUM AND MINIMUM DOSES AND THE PERCENTAGE VARIATIONS, IN ALL CASES OBSERVED, REGARDLESS OF PRESENCE OR ABSENCE OF FIBRILLATION

Effect Produced	Preparation	No of Cases	Average Dose	Maximum Dose	Percentage Above	Minimum Dose	Percentage Below
Best	Tinctures	21	0.095	0.150	57	0.039	59
	Infusions	3	0.087	0.096	10	0.072	18
	Digitoxin	13	0.040	0.0637	59	0.026	35
Rapid without nausea or vomit	Tinctures*	17	0.123	0.223	78	0.051	60
	Infusions	5	0.133	0.227	70	0.102	24
	Digitoxin	7	0.062	0.079	27	0.043	23
Rapid or vomiting	Tinctures	10	0.204	0.350	71	0.127	38
	Infusions	4	0.144	0.186	29	0.115	20
	Digitoxin	10	0.074	0.110	48	0.038	49
Therapeutic, all cases	Tinctures†	25	0.148	0.293	97	0.051	66
	Infusions	8	0.141	0.227	69	0.102	28
	Digitoxin	15	0.066	0.110	66	0.038	43
Total taken	Tinctures‡	9	0.239	0.368	53	0.179	26
	Infusions	3	0.191	0.272	42	0.115	40
	Digitoxin	5	0.096	0.127	32	0.073	23

* Exceptional Case 17 omitted. If included, average becomes 0.146 cat units per pound.

† Exceptional Case 17 omitted. If included, average becomes 0.159 cat units per pound.

‡ Exceptional Case 17 omitted. If included, average becomes 0.259 cat units per pound.

variation which are encountered in the determination of the human doses of digitalis and digitoxin.

In Table 6 all of the observations made with tinctures and infusions of digitalis and with digitoxin are brought together irrespective of the question of fibrillation. In this table, which is virtually a composite of the preceding two, the greatest variations from the average doses do not differ very materially from those already discussed, although this grouping together of all of the cases somewhat increases the range of variation.

We have so far dealt only in terms of the greatest variations from the averages in the several instances and have thus placed our subsequent remarks regarding the actual dosage of digitalis for man, as based on our figures, in the least favorable light. For detailed con-

sideration we will confine our attention to the dose which was found necessary for the production of the full therapeutic effects or of one or another of the minor toxic actions of the drug, as this is the dose which we usually desire to give to any patient who requires treatment by digitalis

THE FULL THERAPEUTIC DOSE IN FRACTIONS OF A CAT UNIT OF ACTIVITY
PER POUND OF BODY WEIGHT

Reference to the average doses stated in tables 4, 5 and 6 for the tincture and the infusion of digitalis and for digitoxin, respectively, in the group classified as "therapeutic, all cases" (including both those showing full therapeutic and those with minor toxic actions) will at once make it evident that there is little essential difference between the doses of the respective preparations dependent on the presence or absence of auricular fibrillation, and the averages for any preparation for all of the cases combined are essentially the same as those for each of the two divisions taken separately. We will therefore first turn our attention to the averages of all the cases, and take up the two main classes later.

If Table 6 be taken in conjunction with Tables 1 and 3 for details, we can make the following deductions:

1 The average dose of the tincture of digitalis required to produce full therapeutic effects or minor toxic actions is 0.148 cat unit per pound of the patient's body weight. This is based on the results of 25 courses of administration of tinctures of widely different relative activities. In eight of these the dose producing these effects fell below the average to an extent not exceeding 15 per cent. of the average dose. In five others the dose required exceeded the average by an amount not greater than 15 per cent. of the average dose. In other words, the doses taken in 13, or 52 per cent. of the cases were divergent from one another by the extreme limit of 30 per cent. of the average dose. One resistant patient required 97 per cent. more than the average dose for the production of effects, while the most susceptible one responded to a dose 66 per cent. below the average.

2 The average dose of the infusion of digitalis was found to be 0.141 cat unit per pound of the patient's body weight. Eight patients were studied in this determination and they received infusions differing considerably in strength. Of these eight patients, two responded to doses not over 15 per cent. less than the average dose, and one required more than the average by an amount not exceeding 15 per cent. On the other hand, one patient required an excess of 69 per cent. over the average to cause the desired effects, while another was susceptible to the extent of showing the full effects from a dose less than the average by 28 per cent.

3 The average dose of 0.066 cat unit per pound of the patient's body weight was established for crystalline digitoxin as the result of its administration to fifteen patients. Of these there were five in whom the response was secured with a dose below the average by an amount not exceeding 15 per cent and a dose not more than 15 per cent above the average was required for the production of effects in three cases. That is, eight cases, or 53 per cent responded to doses varying from one another by not more than 30 per cent of the average dose.

4 These three statements may be epitomized by saying that an analysis of 48 courses of administration of digitalis preparations showed that, irrespective of the activity of the preparation used and without relation to the presence or absence of auricular fibrillation, approximately half of the doses fell within 15 per cent of the average established in terms of the activity of the drug in fractions of a cat unit per pound of body weight of the patient.

The full therapeutic or minor toxic doses of these same preparations, as shown in Tables 4 and 5 for fibrillating and non-fibrillating cases, respectively, have been analyzed in the same way and the results are so closely similar to those just reported for the combined table that it is not necessary to detail them. The remaining average doses for any of the preparations employed, and for cases with or without auricular fibrillation, and for all of the cases together, are set forth in the three tables—4, 5 and 6—and further discussion of them seems unnecessary in this place. They are there for reference, and I shall leave them without further mention except in connection with the subsequent discussion of certain other aspects of our problem.

5 If the therapeutic doses for both tinctures and infusions be taken together as representing the dose of digitalis, the average of the thirty-three courses of administration is 0.146 cat unit per pound of body weight. This will be regarded as the established average dose for digitalis inasmuch as the infusions and tinctures give practically identical figures.

THE MAXIMUM DOSES BORNE WITHOUT DANGEROUS EFFECTS

In any determination of the dose of such a drug as one of the digitalis bodies, in which the administration of sufficient amounts is often a matter of life or death, it would not be enough to fix a dose which could usually be expected to produce therapeutic effects, and it is quite as essential to have some idea of the maximum amount which a patient may be expected to take without suffering injury. These records provide some information along this line, for in some instances the drug was pushed to the point of appearance of some symptom of mild toxic

action when the therapeutic dose had been borne without such manifestation

In all there were nine instances in which the tincture of digitalis was given in amounts in excess of the full therapeutic dose. Among these nine cases there were three in which at least 50 per cent more than the average full therapeutic dose was given; two in which approximately 50 per cent more than this dose was given without so much as the production of emesis, and there was one patient who took nearly 300 per cent of the average therapeutic dose without the least evidence of any toxic action whatever (Case 17 in Table 3). In none of these cases was there any evident detrimental effect from the digitalis.

In three cases the infusion of digitalis was also given in amounts exceeding the requirements for the production of full therapeutic effects, and one of these took nearly double the average dose without manifesting so much as nausea.

Finally, there were five cases in which the therapeutic dose of digitalis was similarly exceeded, in one the dose was nearly double, in another more than $1\frac{2}{3}$ times the average. In none of the five cases were the excessive doses provocative of more annoying symptoms than nausea and vomiting.

Among all seventeen instances in which one or another preparation of digitalis had been taken in excess of the full therapeutic dose, there was only one instance in which the largest dose borne fell as low as the average therapeutic dose, and in this single case the dose was only 18.5 per cent below the average.

It is obvious from the preceding discussion that, were we to take the calculated average therapeutic dose as our guide in the administration of digitalis we would run little or no risk of administering a dose which might in any way threaten life.

INFLUENCE OF THE ACTIVITY OF THE PREPARATION OF DIGITALIS ON THE DOSE FOR MAN

It must already be apparent to the reader that the activity of the digitalis leaf from which either a tincture or an infusion is made has no influence on the dose of the resulting preparation if this is measured in terms of the cat unit of activity. Of course the activity of the preparation does have a marked influence on the gross measure of the amount of the preparation which must be given, for either the single doses or the total dose required, when measured in cubic centimeters or in minims or drams.

INFLUENCE OF THE CARDIAC CONDITION ON THE DOSE IN TERMS
OF FRACTIONS OF A CAT UNIT PER POUND

Attention has already been called to the fact that the dose required for the production of the full therapeutic effects is essentially the same for any given preparation irrespective of the presence or absence of auricular fibrillation. Throughout this entire series of observations there is no evidence of any relation between the dose required for the production of a given effect and the cardiac condition of the patient. Even in cases in which the heart was not primarily at fault the doses fell within the usual limits established for those in which the heart was the essential offender. Thus, in Table 3, Case 1, the patient showed scarcely any failure of cardiac compensation, and had an old standing mitral leak with associated stenosis apparently of slight grade, the patient in Case 3 had chronic pulmonary tuberculosis and tuberculous peritonitis, the patient in Case 4 was primarily suffering from chronic nephritis, in Case 15 the patient had both chronic nephritis and diabetes mellitus. In the same table the patient in Case 23 was suffering mainly from overwork and mechanical strain of his heart, Patient 31 had chronic interstitial nephritis and mitral stenosis and insufficiency, Patient 32 had chronic cirrhosis of the liver and chronic myocarditis, and Patient 33 chronic syphilitic aortitis.

INFLUENCE OF SEX AND AGE ON THE DOSE

The total number of courses of administration of digitalis (exclusive of the pure principles) amounted to 33, as already stated, and the average therapeutic dose established from these observations is 0.146 cat unit per pound. Nine female patients gave an average dose of 0.167 cat unit per pound, and 24 male patients 0.138 cat unit. The average dose for the females was only 14 per cent above that for all of the cases, and that for the males only 6 per cent below. It seems probable that a larger number of cases in both groups would have brought their respective averages even closer to the average for all cases. These facts are presented for what they may be worth.

Analyzing these 33 courses of administration of digitalis from the point of view of age, excluding the two children who required 0.104 and 0.130 cat unit, respectively, the difference in dose due to age is found to be slight. The average dose for patients over 40 years of age is only 5 per cent above, and that for the patients of 40 or younger only 13 per cent under the average for all cases. It seems, therefore, that neither age nor sex plays any important part in influencing the dose of digitalis, when this is measured in terms of the cat unit of activity of the drug per pound of the patient's weight.

INFLUENCE OF SIZE AND STATURE ON THE DOSE

Excluding from consideration in this connection the two children, the 31 cases receiving digitalis are divisible into three groups from the point of view of size and stature of the patients. Inasmuch as there was no very obese patient in the entire series, the body weight is a good index of general stature. A group of five patients in which the weight lay between 100 and 125 pounds gave an average therapeutic dose of 0.142 cat unit per pound. Twenty patients ranging from 126 to 150 pounds in weight gave an average dose of 0.141 cat unit per pound. And six patients in which the weight was more than 150 pounds showed an average dose of 0.176 cat unit. Among the six heavy patients only two responded fully to doses less than the established average for all cases. Although the higher figure for the group of heavier patients may be rather more than a mere coincidence, more extended observation is required before any definite statement can be made on this point.

All of the weights stated in the tables were the lowest recorded for each patient, and always represented as nearly as possible the actual weight of the individual after all edema had disappeared. When it was impossible to remove the edema, an allowance was made for the estimated weight of the fluid present, this allowance being based on the actual losses which occurred in other patients. If such an allowance is not made the estimated required dose will usually be decidedly too high. Adipose tissue has almost the same significance as water so far as its influence on the functions of the body are concerned (excepting heat conservation) and it is probable that a similar allowance would have to be made in the calculation of the dose required for a very obese person. This is supported by Hatcher's observation⁹ that very fat animals are more susceptible to digitalis in proportion to their weight than are ordinary ones.

RATE OF ABSORPTION OF DIGITALIS AND DIGITOXIN

Most of the earlier patients received the drug in much smaller single doses than I later learned to give, so that the time before the onset of the action of the drug might be expected to have averaged longer among these than among those who received the larger individual doses. The cases have therefore been divided into two groups and Table 7 gives the results of their analysis.

The table shows the marked effect of the size of the individual dose on the time that must elapse before the actions of digitalis or digitoxin can manifest themselves, and it is obvious that if we desire to induce effects rapidly by oral administration we must resort to doses as large as can safely be borne. Cushny⁴ has said, "One great limita-

tion in the use of digitalis is caused by the slowness with which its action is elicited. Rarely is any distinct change to be seen before the fourth day of treatment, and this precludes its use in the most acute cases." This is the prevalent idea among clinicians and to be found in the text-books. That it is incorrect seems so obvious that it is a matter of surprise to find that very few have taken exception to it. One clinical investigator⁵ has recently said that by the use of large doses, up to two drams of the tincture of digitalis (B. P.) daily, nausea and beneficial cardiac effect could be produced in from thirty-six to forty-eight hours. To this I can add from my own experience that I have not infrequently succeeded in producing full therapeutic effects from the oral administration of digitalis or digitoxin in from twelve to eighteen hours after the first dose was given, and could

TABLE 7—SHOWING AVERAGE TIME FROM FIRST DOSE TO ONSET OF EFFECTS OF DIGITALIS AND DIGITOXIN

	Individual Doses	Earliest Effects		Full Therapeutic Effects	
		Number of Cases	Average Time in Hours	Number of Cases	Average Time in Hours
Digitalis	{ Small	8	38	19	70
	{ Large	16	13	12	28
Digitoxin	{ Small	5	42	7	84
	{ Large	8	15	8	33

induce these effects in the majority of cases in about twenty-four hours by the use of large doses adjusted to the patient's needs on the basis of the cat unit of activity of the preparation and the weight of the patient. On this basis I have given single doses of the tincture of digitalis ranging from 8 to 15 c c, of the infusion, an initial dose of 50 c c, and have used single doses of crystalline digitoxin of from 1.0 to 1.75 mg. As shown in Table 7, the average time for the development of the full therapeutic effect after digitoxin has been given in large individual doses is less than thirty-six hours, and the full effects have been secured in as little as twenty hours on more than one occasion. It seems probable, with a better understanding of the dosage of this principle, that its full action can be secured quite as rapidly as that from the galenical preparations of digitalis. The statements in the literature concerning the phenomenal toxicity of digitoxin and its peculiar slow development of action seem to have been somewhat misleading.

THE COMPARATIVE ABSORPTION OF DIGITALIS AND DIGITOXIN FROM
THE ALIMENTARY CANAL OF MAN

Aside from the general knowledge that the oral administration of these drugs usually produces the effects associated with their absorption we have relatively meager information on this important question, so far as it concerns man. I have already cited the observations of Bailey,⁷ Hatcher and Bailey,⁸ and Hatcher⁹ that ouabain, strophanthus and the strophanthins are absorbed from the alimentary canal of either man or animals in a very variable manner, but for the most part both slowly and incompletely. From repeated observations which Dr Hatcher and I have made in the laboratory we have come to the conclusion that this is also true of many other digitalis bodies, among which the true digitalin of Kiliani is to be included.

The dose of true digitalin is variously stated by different observers, and New and Nonofficial Remedies for 1914 says that some authorities give the same doses as for crystalline digitoxin (0.25 mg or 1/250 grain) while others give much larger doses. Klingenberg¹⁶ could not secure any very marked effects from doses up to 15 mg daily, and I have given as much as 48 mg daily to a patient for more than four days before the full therapeutic action was secured. On the other hand only about one-sixth of this amount proved adequate for another patient. In terms of cat units per pound the largest dose required for full therapeutic action was 7.6 times as great as that of digitoxin. In view of this apparent lack of absorption I abandoned the use of true digitalin and have made no attempt to establish its dose.

My experience with digitalein is rather similar to that just recorded, and as this is not a pure principle and is not of uniform composition I have omitted it from these studies. We may, therefore, confine our attention to digitalis as a whole and to digitoxin.

It is obvious from the fact that it has been possible to fix a dose for each of these preparations, from which the range of variation is not very great in spite of the many complicating factors, that both of them are absorbed from the alimentary canal of man in a fairly uniform manner. Both seem also to be absorbed with considerable rapidity, as is demonstrated by the fact that the full therapeutic effects can be induced within comparatively few hours after the administration of the first dose. When the administration of either drug is stopped at once after the appearance of minor toxic symptoms or the evidences of full therapeutic action there is little or no increase in either group of phenomena. In fact, if the administration is checked

16 Klingenberg Ueber die klinische Bedeutung des Digitalinum verum, Arch f exper Path u Pharm, 1894, xxxiii, 353

at the appearance of nausea, vomiting often fails to appear. Both of these facts indicate that the absorption is completed in a relatively short time. Prompt and efficient absorption seems also to take place even in the face of considerable abnormality of the alimentary canal, for patients manifesting evidence of marked congestion of this region, resulting even in repeated vomiting, respond quite as promptly and to the same doses as do those who are apparently free from disturbance. A case in point is Case 4, under Report of Illustrative Cases.

The establishment of the fact that both digitalis and digitoxin are usually promptly and fairly uniformly absorbed in man does not prove, however, that they are absorbed with equal rapidity or to an equal extent and the following seems to show that such is actually not the case.

Hatcher⁹ has shown that the several digitalis bodies are mutually and quantitatively synergistic in their actions on the heart in the cat and other animals. If the fatal vein dose be established for digitalis and digitoxin, respectively, in the cat and then each of several other cats be given 50 per cent of the fatal dose of one of these, it will require an amount of the other to cause death which is 50 per cent of its fatal dose. In other words 50 per cent of the fatal vein doses of each of these two preparations is equivalent to 100 per cent of the fatal dose of either. If, therefore, digitoxin and digitalis were absorbed to an equal extent from the alimentary canal of man the doses of these two, in terms of fractions of a cat unit per pound, should be the same for the production of the same degree of action. The results of the present observations show that such is not the case. Thus, the therapeutic dose of digitalis is 0.146 cat unit per pound while that for digitoxin is only 0.066 cat unit. In other words, in terms of activity it requires 2.21 times as much digitalis as of digitoxin to produce the same effect when both are given orally to man.

The leaf from which Tincture 97 was made was assayed by C. E. Vanderkleed and found to contain 0.31 per cent of digitoxin. Eleven patients weighing 1,543 pounds total required 21,700 mg of this leaf for the production of full therapeutic effects, giving an average of 14 mg per pound. This is equivalent to 0.0434 mg of digitoxin per pound. Fifteen patients required an average of 0.023 mg of crystalline digitoxin per pound for the production of a similar effect. On the basis of weight of digitoxin these figures show that when given in the form of the tincture of digitalis 1.88 times as much digitoxin was required for the production of a given effect as when the pure digitoxin itself was given. We may account for this fact in one of two ways. Either on the ground that there must be some substance present in digitalis and soluble in both alcohol and water (tincture and infusion) which

acts to delay the absorption of the digitoxin present. Or by supposing that the digitoxin in the leaf and its galemlal preparations is present either in a different form from that in which we know it after isolation, or is bound to some other substance in a way which permits of the liberation of only a portion of it for absorption. This latter would seem to be the more plausible explanation in view of the complexity of plant constituents.

This fact also serves to confirm the belief that the chemical assay of digitalis, in which the digitoxin content is determined, does not provide results which can be translated into doses for man, and it gives a rational explanation for this deficiency of the method.

METHODS OF STANDARDIZATION COMPARED WITH REFERENCE TO THEIR APPLICABILITY TO THE DETERMINATION OF DOSAGE FOR MAN

In another paper¹⁷ I have discussed the relative merits of the several biologic methods of standardizing digitalis preparations, and there made the statement that one of the desiderata of any method should be that, "The results of the evaluations should be more or less fully transferable to man." At the conclusion of the paper I expressed the opinion that the cat method of Hatcher attained this end. This opinion was based mainly on critical analysis and was little supported by clinical observation, except in a few details. The results of the present work now seem to have established this as a fact. There are, however, other methods of standardization, at least one of which is quite widely accepted—the one-hour frog method. Dr. Hatcher and I have contended that by this, or any other method in which absorption of the drug is an essential feature, it would be impossible to compare the activities of two different samples of a complex substance like digitalis in a way which would give results transferable to man. I am now in a position to offer confirmation for this contention.

The leaves from which Tinctures 97 and 150 were prepared were found by Vanderkleed to contain 0.31 and 0.27 per cent of digitoxin, respectively. In terms of digitoxin, therefore, the former was 1.14 times as active as the latter. The frog test showed Tincture 97 to be 1.19 times as active as Tincture 150. On the cat Tincture 97 proved to be 1.54 times as active as Tincture 150, and on man, based on the number of milligrams of the leaf per pound of body weight which was required to produce therapeutic effects, the former was 1.71 times the latter in activity. The accompanying tabular presentation (Table 8) shows these relations more clearly.

¹⁷ Eggleston, Cary. Biological Standardization of the Digitalis Bodies by the Cat Method of Hatcher, *Am Jour Pharm*, 1913, lxxxv, 99.

Here the chemical determination and the one-hour frog tests gave similar ratios of activity for the two specimens, but between these ratios and those determined on the cat and on man there is considerable divergence. On the other hand, the ratio of activity established by the cat is very nearly the same as that found to hold for man. It must be borne in mind that in the case of the dose of Tincture 150 we have only three observations, the average of which happens to be higher than that for digitalis in general, as founded on a large series. If there had been a larger number of cases treated with this tincture the average dose would almost certainly have approached that for digitalis, namely, 0.146 cat unit per pound. Had this been the case, the ratio of activity between Tinctures 97 and 150, as based on the number of milligrams of the leaf taken per pound, would have fallen to from 1 to 1.57, almost exactly that determined on the cat. The facts, discarding this suggested correction, certainly show that the ratio

TABLE 8—RELATIVE ACTIVITY OF TWO TINCTURES OF DIGITALIS PREPARED FROM LEAVES CONTAINING VARYING AMOUNTS OF DIGITOXIN

In Terms of Acidity as Determined	Tincture 97		Tincture 150
Chemically	1 part	equals	1.14 parts
On frogs	1 part	equals	1.19 parts
On cats	1 part	equals	1.54 parts
On man	1 part	equals	1.71 parts

of activity determined on the cat is much more nearly that for man in the case of digitalis, than is the ratio similarly determined with the same specimens by either the frog or the chemical methods of standardization.

When it comes to the comparison of the relative activity of a sample digitalis with that of digitoxin all methods fail to give results which are transferable to man on account of the peculiarity of the absorption of digitoxin from the galenical preparations of the leaf. Thus, by the frog, digitoxin would be 247 times as active as the leaf of Tincture 97 and 277 times as active by the cat test, but it proved to have been 606 times as active on man. This failure of the several methods was anticipated, and we have held from our animal experiments that such was necessarily the case. This in no way conflicts with the contention that the cat method is the best suited for the determination of the relative activity of different digitalis bodies after they have gained entrance into the circulation.

Before passing to the summary and conclusions to be drawn from these observations I should like to record a method of practical application of their results which naturally suggests itself.

PRACTICAL APPLICATION

It would be desirable to prescribe a preparation of digitalis which had been standardized by the cat method, but if this was not obtainable one could proceed on the basis that a high grade leaf had an average cat unit strength of 100 mg, and the cat unit should then be used as the basis for the calculation of the probable required dose. In the case of an average first-class tincture 0.145 c c could be taken as the average therapeutic dose for each pound of the patient's body weight. On the basis of the patient's actual or estimated weight the total amount which would probably be required should be calculated and this quantity could then be divided into single and daily doses according to the rapidity with which it was desired to induce the full therapeutic effects. If after the total calculated amount had been taken the patient failed to show the full therapeutic effect, or some minor toxic action indicating that enough had been given, the administration should be continued in small repeated doses until one or the other of these evidences called for its withdrawal.

In this way it is possible to give a third to half of the total calculated therapeutic dose at a single administration, to follow this in from four to six hours with a quarter to a third of the total dose, and to give the remainder in a few doses of smaller size at intervals of from four to six hours. By this plan of administration the full effects can be secured in from twelve to thirty-six hours in the majority of cases.

The administration of half of the total dose may call for the giving of from 5 to 15 c c of the tincture at once, and it might be feared that such a large dose might cause gastric irritation and nausea or vomiting. I have given such doses repeatedly since the completion of the greater portion of this work and have never seen the least disturbance of any kind arising as a consequence. This is due to the fact that the nausea and vomiting following the administration of the digitalis bodies is of central origin and results only after the absorption of a sufficient quantity of the drug into the circulation. Dr Hatcher and I have previously shown this to be true for both man and animals¹⁸.

The same plan could be carried out with digitoxin, which is approximately of uniform activity, the average dose per pound for man being 0.023 mg. It would be better to employ this preparation in the form of tablet triturates, as fairly strong alcohol is required for its

¹⁸ Hatcher, Robert A., and Eggleston, Cary. The Emetic Action of the Digitalis Bodies, *Jour Pharm and Exper Therap*, 1912, iv, 113. Eggleston, Cary, and Hatcher, Robert A. The Emetic Action of the Digitalis Bodies, *Jour Am Med Assn*, 1913, ix, 499. Eggleston, Cary. Clinical Observations on the Emetic Action of the Digitalis Bodies, *ibid.*, 1913, ix, 757.

solution and the evaporation of some of the solvent might lead to such a concentration of the solution that a dangerous miscalculation might result, or the substance might become partly precipitated

It should be reiterated in this place that the use of such large doses of either digitalis or digitoxin as are here mentioned is not a safe procedure unless the patient can be under nearly constant observation and unless the effects of the treatment can be graphically recorded at frequent intervals. This practically limits such procedures to hospital practice and to those well versed in the significance of polygraphic and electrocardiographic records

An interesting bit of evidence may be introduced here which tends to confirm the correctness of the preceding statements of average doses. It might be added that this confirmation was quite unexpected. In a paper on the emetic action of digitalis¹⁸ I reported a considerable number of courses of administration of digitalis which were carried to the production of nausea or vomiting. In all of these cases the daily doses given were rather small and the administration was continued over a considerable period of time, so that the doses taken were almost certainly a little in excess of the minimum which would have been needed had larger daily doses been given. The doses taken were known in terms of grams of digitalis leaf for each of the cases. In 68 first courses of administration the average dose per patient was 3,666 mg of leaf. On the basis of 150 pounds as the average weight of an adult this would have amounted to an average dose of 30.5 mg of leaf per pound of body weight. We have tested a large number of different samples of digitalis in the laboratory and have established 120 mg as the cat unit of the average specimen of digitalis of commerce. With this as the activity the average emetic dose for the 68 cases would be 0.203 cat unit per pound. The 14 instances of nausea or vomiting in Tables 1 and 3 of this article give an average emetic dose of 0.187 cat unit per pound. These two figures are very similar in view of the difference in the methods of observation employed in the two series of cases providing them.

SUMMARY

1 The confused state of our knowledge of the dosage of the digitalis bodies has been set forth

2 A series of observations has been reported and the results subjected to analysis from several points of view for the purpose of gaining some information on the subject of the dosage of these bodies for oral administration to man, and from these observations and analyses the following conclusions and deductions can be offered

CONCLUSIONS AND DEDUCTIONS

1 The cat method of standardization of digitalis yields results on which the dose for man can be based

2 The average therapeutic dose of digitalis, given orally to man in the form of the tincture or infusion, is 0.146 cat unit or about 0.146 c.c. of an average high-grade tincture per pound of body weight, as established by thirty-three observations

3 Fifteen observations have established 0.066 cat unit, or 0.023 mg., per pound as the average therapeutic dose of crystalline digitoxin

4 In approximately half of a total of 48 courses of administration of either digitalis or digitoxin, full therapeutic effects were secured with doses falling within 15 per cent. above or below the average dose

5 Doses considerably larger than the average were taken in 17 instances without the production of more than mild toxic symptoms

6 The activity of the preparation of digitalis has no material influence on the dose required in terms of cat units

7 Age, sex, and cardiac condition do not seem to influence the size of the dose required

8 Both digitalis and digitoxin are probably rapidly and fairly uniformly absorbed from the alimentary canal of man, but digitalis is less completely absorbed than is digitoxin

9 Strophanthus, the strophanthins, ouabain, true digitalin, and some other digitalis substances are poorly or irregularly absorbed when given by mouth to man or to the higher animals and are unsuited for therapeutic use in this way

I wish to acknowledge the help I have derived in the course of this work from many profitable discussions with Dr. Hatcher. Dr. C. E. Vanderkleed's cooperation in supplying me with digitalis leaves, the digitoxin content of which he had determined, is also much appreciated. I have, finally, to thank the attending and house staffs of the Second Medical Divisions of Bellevue and of City Hospitals, respectively, for their cordial cooperation in providing me with the cases for this study. I should like to mention, in particular, Dr. E. P. Shelby of the City Hospital and Dr. Warren Coleman of Bellevue Hospital attending staffs without whose generous aid I should not have been able to have made these observations for want of sufficient clinical material.

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THE DIAGNOSTIC VALUE OF URIC ACID DETERMINATIONS IN BLOOD *

PROF OTTO FOLIN AND W DENIS, PH D
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Ever since the description by Garrod in 1860 of his so-called thread test for uric acid in gouty blood, the finding of an excess of uric acid in the blood of patients suffering from joint diseases has been considered to point toward a diagnosis of gout. Within recent years Brugsch and Schittenhelm¹ have stated that in normal human blood uric acid is absent. Its presence they consider as pointing to the existence of gout. This view has also been accepted by Gudzent² who recommends his dialysis method for the detection of uric acid in blood as being of aid in the differential diagnosis of joint conditions.

That Brugsch still believes in the diagnostic value of uric acid tests is shown by the recent appearance of a paper from his laboratory³ describing a clinical method for the determination of this substance in blood. According to this procedure a few drops of serum are treated in a special test tube by means of our phosphotungstic acid reagent. Sodium carbonate is then added and the blue color obtained is read against a permanent standard. Coming from Brugsch such a method will doubtless receive considerable attention, and will lead to much useless and misleading work. All blood contains varying amounts of phenols, which also give a blue color with our phosphotungstic acid reagent, indeed, in some cases these bodies will give from two to three times the amount of color produced by the uric acid present in the blood. In our method the uric acid is precipitated and thus separated from the phenols. We realize that the determination of uric acid in blood by our method is still probably outside the range of most clinical laboratories, but we are convinced that all "short cut" methods so far proposed are bound to lead to grossly misleading results.

By means of our technic we were able to show about three years ago that 100 c c of normal human blood contains 1.5 to 2.5 milligrams of uric acid, and that in gout, lead poisoning, leukemia, and in some cases of nephritis this amount was greatly increased.

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* From the Chemical Laboratories of the Massachusetts General Hospital and Harvard Medical School.

1 Brugsch and Schittenhelm *Ztschr f exper Path u Therap*, 1907, iv, 438, 446, 480, 532, 538, 551.

2 Gudzent *Deutsch med Wchnschr*, 1912, xxxviii, 603.

3 Brugsch and Krysteller *Deutsch med Wchnschr*, 1914, xl, 746.

From the results of our quantitative uric acid determinations in normal human blood it became clear at once that the various qualitative tests for uric acid, from Garrod's naive thread test down to the elaborate recent procedures of Schittenhelm and of Gudzent are all equally treacherous and useless for differential diagnostic purposes. The value of exact quantitative determinations of the uric acid for such purposes seemed, on the other hand, to rest on a sound foundation of facts. The accumulation of relatively immense urate deposits in the joints of persons suffering from gout would seem to be almost conclusive proof that the circulating fluids of such patients must be particularly rich in urates in comparison with the blood of those in whom such deposits of urates never occur. The blood of normal persons has, however, been found to carry far more uric acid (1-2.5 mg per 100 c c) than was formerly suspected, and the difference in the uric acid content of such normal blood and the blood of those suffering from gout is materially smaller than earlier investigators realized. Since it is by no means excluded that the blood in diseases other than gout may not, occasionally at least, carry more than the normal amount of uric acid, the diagnosis of gout by means of uric acid determinations is by no means so simple or certain that numerous and serious blunders will not occur. In the course of several hundred uric acid determinations made on many different kinds of human blood during the past three years we have become convinced that even exact quantitative uric acid determinations are not by themselves an adequate protection against frequent mistakes in the differential diagnosis of gout and other joint diseases.

In our earlier work we were struck by the fact that there is apparently no constant relationship between the amount of uric acid and the amount of nonprotein nitrogen in human blood. The variations found are very much greater than the corresponding variations (between the uric acid and the total nitrogen) met with in urine on a given, definite diet, and seemed to be due to a selective excretory activity on part of the kidneys. In respect of these two factors, the uric acid and the nonprotein nitrogen, there manifestly can be four distinctly different classes of human blood.

- 1 Blood in which both uric acid and nonprotein nitrogen are present in normal amounts

- 2 Blood in which with normal amounts of uric acid we have greatly increased amounts of nonprotein nitrogen

- 3 Blood giving abnormally high uric acid values with normal amounts of nonprotein nitrogen

- 4 Blood in which abnormally large amounts of both uric acid and nonprotein nitrogen are present

Examples of each of these classes are given in the accompanying tables

TABLE 1, CLASS 1

NORMAL URIC ACID AND NORMAL NONPROTEIN NITROGEN

No	Diagnosis	Milligrams per 100 c c	
		Nonprotein Nitrogen	Uric Acid
	Normal man	32	20
	Normal man	24	20
107	Alcoholic gastritis	34	20
147	Cystinuria	28	14
9	Diabetes insipidus	25	15
144	Cardiorenal disease, arteriosclerosis	26	28
P6	Insanity	32	24
P6	Insanity	24	20
P6	Insanity	28	20
P6	Insanity	28	24
S8	Arteriosclerosis	30	25
S9	Chronic interstitial nephritis	27	26
S10	Chronic interstitial nephritis	30	25

TABLE 2, CLASS 2

NORMAL URIC ACID AND HIGH NONPROTEIN NITROGEN

No	Diagnosis	Milligrams per 100 c c	
		Nonprotein Nitrogen	Uric Acid
10	Nephritis, prostatectomy	110	23
R16	Infectious arthritis (purin free diet for two days)	89	18
R14	Bone tuberculosis (purin free diet for two days)	102	16
R18	Acute rheumatic fever (purin free diet for two days)	104	17
R19	Acute rheumatic fever, pericarditis	100	16
R36	Mitral stenosis (purin free diet)	60	22
T1	Arthritis deformans	54	12
T9	Arthritis deformans	50	20
T20	Infectious arthritis	80	23
T26	Arthritis	50	20
58	Acute infectious arthritis (purin free diet)	80	19

TABLE 3, CLASS 3

HIGH URIC ACID AND NORMAL NON-PROTEIN NITROGEN *

No	Diagnosis	Milligrams per 100 c c	
		Nonprotein Nitrogen	Uric Acid
1	Typical gouty attacks for past seven years	25	38
3	Arteriosclerosis Acute gout, first attack	40	34
4	Alcoholic gastritis and gout	40	35
5	Gout, many tophi	30	44
6	Typical gout last attack two years ago	28	52
12	Has passed several vesical calculi consisting of pure uric acid	30	52
L1	Typical gout in both great toes	36	54
D3	Acute gout, many tophi, arteriosclerosis	32	31
L6	Acute gout, many tophi, large urate ulcer	42	51
L	Normal man, many members of whose family have been gouty	29	40
49	Swollen joints, probable gout	28	50
106	Swollen and painful joints, probably gout, no tophi	30	33

* Purin-free diets for at least two days before blood was taken

TABLE 4, CLASS 4
HIGH URIC ACID AND HIGH NONPROTEIN NITROGEN

No	Diagnosis	Milligrams per 100 c c	
		Nonprotein Nitrogen	Uric Acid
82	Uremia	288	95
97	Uremia	284	66
28	Uremia	125	100
76	Uremia	228	75
R16	Arthritis deformans (purin free diet for two days)	104	38
R32	Weak heart, edema of lungs, hypertrophic arthritis	90	50
38C	Pneumonia	72	50
78C	Cardiorenal case	326	44
77C	Chronic nephritis	148	65
29C	Nephritis following eclampsia	100	41
T3	Arthritis deformans	62	70
T22	Acute gonorrheal arthritis	124	33
T32	Arthritis deformans	59	36
L4	Acute gout, tophi, chronic interstitial nephritis (purin free diet)	60	57

The last three tables represent three chemically different kinds of abnormal blood

Gout, as will be seen from Table 3, is characterized by abnormally high uric acid content of the blood *without* any abnormally high accumulation of other nitrogenous waste products (nonprotein nitrogen). Exceptions may of course occur, gouty patients may also have nephritis. Nephritis in the gouty is usually of the arteriosclerotic type, a type which according to our experience is not accompanied by an excessive accumulation of nonprotein nitrogen in the blood (except in the terminal stages of the disease). This rule is, however, unfortunately not without exceptions. The last case quoted in Table 4, of gout and interstitial nephritis, showed a high nonprotein nitrogen (60 mg) as well as a very high uric acid (57 mg).

From an inspection of Table 3 and by comparing the figures and diagnoses there given with the figures and diagnoses of Tables 2 and 4, it will be seen that to be of material help in the differential diagnosis of gout the uric acid determinations must be accompanied by determinations of the nonprotein nitrogen. In joint diseases other than gout it is by no means uncommon to find uric acid values nearly if not quite so high as in gout. In arthritis, however, a high nonprotein nitrogen is even more frequent than a high uric acid. Indeed, in this respect the blood in arthritis frequently resembles the blood of glomerular nephritis.

In making use of blood analysis to decide whether a given doubtful case of joint disease is gout or arthritis, it is therefore absolutely necessary to determine the nonprotein nitrogen (or at least the urea) in the blood as well as the uric acid. And before the blood is drawn for such analyses it is indispensable that the patient should have been

on a purin-free diet for at least two days. The level of the protein metabolism should also be ascertained by means of a nitrogen determination in the twenty-four hour urine passed during the last day of the experiment.

SUMMARY

1 In gout the blood is almost invariably abnormally high in uric acid, while the other waste products represented in the nonprotein nitrogen of the blood are usually within the normal limits. In arthritis also the blood is not infrequently abnormally high in uric acid, but most such cases have abnormally high nonprotein nitrogen as well.

2 Neither qualitative tests for uric acid in the blood nor quantitative determinations of the uric acid alone can be depended on in the differential diagnosis of gout and other joint diseases.

3 For a differential diagnosis in doubtful cases of gout or arthritis by means of blood analyses the patient must be put on a purin free diet and uric acid determinations must be accompanied by determinations of the nonprotein nitrogen (or urea).

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A CASE OF OPEN DUCTUS ARTERIOSUS (BOTALLI), WITH NECROPSY †

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A case of open ductus Botalli in a girl of 17, with necropsy occurring at the Peter Bent Brigham Hospital in the last year, was carefully observed on Dr Christian's service in the hospital for fifteen days, and notes were obtained of a previous examination four years before entrance. Diagnosis of the lesion was made during life. The completeness of the record of this case gives it that value as an aid to the diagnosis of the lesion which is common to all carefully observed single cases. The purpose of this paper is to present and comment upon this case, to summarize the recent uncollected cases, and to consider such points as these data seem to throw light on, but to make no attempt to repeat the general discussion of the subject so fully presented by Hochsinger,¹ Wells,² Abbott,³ and Goodman⁴

In 1908 H G Wells collected all the uncomplicated cases of open ductus Botalli and found a total of forty-one, only twenty of which were in adults. Maude Abbott, in the same year, found thirty-seven, only nineteen of which had clinical histories, and three of these latter cases were unconfirmed by necropsy. E H Goodman, in 1910, determined the percentage occurrence of symptoms in thirty-four necropsied cases. It is not possible to tell from these papers how many cases confirmed by necropsy and carefully recorded clinically have occurred in adults, but the number is evidently extremely small.

Dr Abbott's and Dr Goodman's analyses of the cases reported are so complete that I have used them in my summary. I have carefully searched the literature for cases occurring since the publication of these papers, and have found twenty-two in all. In only five was the patient over 1 year old, one of these cases was complicated by slight aortic and mitral stenosis, and one by mitral stenosis with acute vegetations, none

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* From the Pathological Laboratory of the Peter Bent Brigham Hospital

1 Hochsinger, K. Zur Diagnose der Persistenz des Botallischen Ganges und der Erweiterung der Lungenarterie, Wiener Klinik, 1907, xxxiii, 311

2 Wells, H G. Persistent Patency of the Ductus Arteriosus Botalli, Am Jour Med Sc, 1908, cxxxvi, 381

3 Abbott, M E. Congenital Cardiac Disease, Osler's Modern Medicine, 1908, iv, 323

4 Goodman, E H. Report of a Case of Patent Ductus Arteriosus Botalli, with a Study of the Cases Heretofore Published, Univ Pennsylvania Medical Bulletin, 1910, xxiii, 509

had other important congenital lesions. Of the infantile cases eleven were complicated by other congenital abnormalities, leaving two uncomplicated infantile cases and two infantile cases in which an absence of other lesions was not noted. The symptomatology and pathology will be discussed after the presentation of the case I have studied.

REPORT OF CASE

Patient—E S, aged 17, female, unmarried, of German ancestry. At the age of 7 the patient had measles, and shortly afterwards mumps. Her general health had been good, she was not subject to tonsillitis or colds, and no other infectious diseases had been noted. There was no history of decompensation symptoms such as dyspnea, edema, or precordial pain. There were no symptoms referable to other organs, with the exception of headaches, occurring about once a week.

In March, 1910, at the age of 13, the patient entered the service of Dr Christian at the Carney Hospital, Boston, and was discharged after thirteen days with the diagnosis of "Congenital heart. Pulmonic stenosis (?) Open ductus arteriosus (?) "

First Examination—On physical examination at entrance, the following heart condition was found. Dulness, the upper border at the third rib, the right border 1 cm to the right of the midsternal line, the left border 3.75 cm to the left of the midsternal line. A palpable thrill over the pulmonic area extended to the left and downward along the left sternal margin. Over the same area was heard a rough systolic rumble running into diastole. A systolic murmur was heard all over the precordia. The pulmonic second sound was accentuated. The action was regular.

March 16 the thrill was noted to be continuous through systole and diastole, but somewhat stronger in systole, with a late systolic accentuation. At the apex could be felt a short late diastolic and a systolic thrill.

June 19 the patient entered the Peter Bent Brigham Hospital on account of "spots on the legs." There had been no general malaise or other symptoms of illness. Four days before entrance a large black and blue spot had appeared spontaneously on the inner side of the right ankle, and soon after several small reddish spots on both shins. The spots had given no noticeable subjective sensations.

Second Examination—A rather poorly developed and nourished girl was found, in no apparent discomfort. The only positive points on physical examination were with reference to the heart and extremities.

The heart examination showed. On palpation, an apex impulse in the fifth space, 8 cm to the left of the midsternal line, over the pulmonic area a marked thrill running throughout the cardiac cycle with greatest intensity during systole, a sharp second sound, distinctly felt, over the pulmonic area. On percussion, dulness with the upper border at the third rib, the right border 2 cm to the right of the midsternal line, and the left border 10 cm to the left of the midsternal line in the fifth interspace. On auscultation, at the apex a first sound of good quality, followed by a systolic murmur somewhat rumbling in character, apparently transmitted from the pulmonic area, a normal second sound, a loud rough murmur over the pulmonic area, running throughout the cardiac cycle coincident with the thrill, with the greatest intensity during systole, a blowing diastolic murmur, distinct from the other murmurs, transmitted from the pulmonic area down along the left border of the sternum, becoming slightly musical in the third and fourth interspaces, aortic second not increased, pulmonic second markedly accentuated, the action regular and moderately rapid. The blood pressure was 118 systolic, 70 diastolic.

Extremities The fingers were clubbed and the nails cyanotic. On the right leg, just above the internal malleolus, was a purplish-black echymosis, about 5 mm in diameter, moderately tender. Scattered over the anterior surfaces of both shins were a number of small purpuric spots 1 to 3 mm in diameter.

The temperature was 103.4, pulse 129, respiration 31. The white count was 14,000, and the hemoglobin 65 per cent. A smear showed moderate achromia, polymorphonuclears 78 per cent, small mononuclears 7 per cent, large mononuclears 15 per cent, eosinophils none. The urine had a small trace of albumin. The Wassermann reaction on the blood serum was negative.

The clubbing of the fingers, with some cyanosis, the character and localization of the thrill and murmurs, and the lack of etiology for cardiac disease, suggested a congenital cardiac lesion, either a patent foramen ovale, or a patent ductus arteriosus. A severe active endocarditis superimposed on the congenital defect was indicated by the purpuric spots, fever, anemia, and heavy sweats, although this indicated infection was considered not necessarily localized in the heart.

Further Clinical Notes—On June 22 examination gave similar heart findings, except that the systolic and diastolic murmurs were noted all over the precordia, and the diastolic murmur seemed of greatest intensity over the aortic area, suggesting a diagnosis of aortic insufficiency in addition to an open ductus arteriosus. The murmur over the pulmonic area is described as a "sawing to and fro murmur" through the whole cycle.

June 23 A high evening temperature, usually reaching 103, continued, but the patient felt comfortable and had no complaints. The purpuric spots had almost faded out.

June 25 Slight cyanosis was noted. Visible pulsations were found in the fifth space, nipple line, in the suprasternal notch, and in the second interspace to the left of the sternum. In the latter spot the impulse was wave-like. The time of maximum intensity was just after the first sound, as judged by apex and aortic pulsations. On percussion no increase of dullness was definite to the right of the sternum, while to the left in the second and third spaces increased dullness was found for a distance from 1 to 2 cm from the sternum. On auscultation the first sound appeared blurred, and was followed by a low-pitched murmur transmitted into the axilla. The rhythm was a protodiastolic gallop. Otherwise the examination revealed no new facts. Another observer the same day noted a distinct capillary pulse.

June 26 The total diameter of the heart was made out by percussion to be 18.5 cm, the left border being 15 cm to the left of the midsternal line at the level of the fifth rib, and the right border 3.5 cm to the right of the midsternal line at the junction of the fourth rib. The apex was most distinct in the fifth space, but could be felt in the sixth. A pistol shot sound was heard in the femoral arteries.

June 27 A distinct systolic thrill at the apex was noted. The diastolic murmur seemed most intense in the third space and the systolic at the apex. A capillary pulse in the fingers and collapsing pulse in the small arteries were plain. The diagnosis at this time was aortic and mitral regurgitation, with possibly a patent ductus arteriosus, and with an acute process on the chronic valvular lesions.

Two blood cultures had showed no growth. Widal reactions were negative. The white count had risen to 34,000. The red count was 2,408,000. Occasional granular casts were found in the urine. The temperature and pulse continued the same course.

The patient's condition now began to grow worse, there was much vomiting, and no food intake. The temperature fell to 99 June 29 and remained about at that level until July 3, when there was an ante-mortem drop.

On July 2 dulness with many fine crackling râles were found at the right base, and the white count was 70,000.

July 3 the systolic murmur was heard in the vessels of the neck, and seemed most intense over the sternum at the level of the third costal cartilage, the diastolic was plainest over the pulmonic area and along the sternum, a capillary pulse, a Corrigan pulse, and pistol shot sounds in the femoral arteries were plainly observed. Cyanosis persisted, and there was dyspnea out of proportion to the temperature.

On July 4, after a comfortable night, the patient sat up in bed suddenly at about 9 o'clock in the morning, with a complaint of palpitation and dyspnea, and quickly became very cyanotic and almost pulseless. The right border of



Fig 1—View of the heart from the left showing the vegetations on the aortic valve (*B*), and a probe in the open ductus (*A*). Beneath the probe can be seen the ridge on the aorta.

the heart was found to be 5 cm (later 6 cm) to the right of the midsternal line. The liver was felt 6 cm below the costal margin and was pulsating. The previously felt thrills had almost disappeared, and the murmurs were of almost the same character, but of diminished intensity. A presystolic gallop rhythm was felt at the apex. The lungs appeared as before. The condition rapidly became worse, with greater cyanosis, deep quick respirations, and very rapid, scarcely audible heart sounds. The patient died at 9 35 a m.

Blood cultures made July 4 showed a growth of an anaerobic hemolytic short-chained streptococcus, probably *Streptococcus viridans*

Necropsy—Two hours' post mortem—Body Emaciated, 165 cm long None but hypostatic discolorations of the skin

Thoracic Cavity When the thorax is opened the heart is found lying in a pericardial sac distended with fluid The apex is in the fifth space, 9 cm to the left of the midsternal line, and the right margin of the ventricle is 6 cm to the right of the midsternal line The plurae are smooth except for a small, easily broken adhesion at the right base posteriorly, and contain no free fluid

Lungs Left, weight 365 gm At the apex is a dry, firm, red nodule 7 cm in diameter The remainder of the lung is crepitant and mottled with dark, brick-red areas on a yellowish ground Right, weight 445 gm The lung appears similar to the left one Microscopically edema is found, with an infarct, and some areas of atelectasis

Heart Weight 252 gm **Right auricle** No dilatation or hypertrophy The foramen ovale is closed Some non-adherent, apparently post mortem, blood clot in the appendage The coronary sinuses normal Tricuspid valve 10.5 cm, leaflets thin and covered with smooth endocardium, not retracted, attached to normal chordae tendinae **Right ventricle** Slight dilatation and hypertrophy, the walls measure 5 mm **Pulmonary valve** 7.5 cm There are only two cusps, which are of equal length, and show no line of former fusion No thickening or evidence of endocarditis can be seen The valve apparently could function A 5 mm orifice, placed 2.5 cm above the origin of the cusps, leads by a tube 8 mm long into the aorta This open ductus Botalli has just within its lumen a vegetation of fresh appearance, and a collection of similar pinkish vegetations from 1 to 3 mm high form a streak leading from the orifice over the surface of the pulmonary artery in a posterior and slightly downward direction The streak is from 1 to 3 cm wide and aside from the vegetative roughenings the endocardium over it appears corrugated and darkened, but not finely irregular The orifice of the ductus has no mound-like elevation about it as was described in Wells' case (Case 6 in the tabular summary) The duct is almost cylindrical in shape, but there is slight narrowing of the lumen near the middle About the aortic mouth and throughout the lumen there is yellowish discoloration but no definite raised patches or sclerosis On the aortic side the duct opens 5 cm above the origin of the aortic valves, just beyond the left subclavian, by an orifice 5 mm in diameter The opening is smooth except for the presence, just below it, of a straight, ridge-like formation 5 mm long and 3 mm high, too stiff and thick to bend and act like a valve Probably this represents the valve-like fold supposed by Strassman⁵ to close the duct when blood pressures change at birth A few vegetations are about this orifice of the duct **Left auricle** Dilated, but not definitely hypertrophied The auricular appendage free from clot **Mitral valve** 9.5 cm, there is slight but definite fibrous thickening of the edges of the cusps, but the endocardium is free from vegetations or ulcerations **Left ventricle** Slight dilatation The walls are 12 mm thick, and the muscle appears normal **Aortic valve** 8 cm Two cusps only are visible, one is 4.7 cm and the other 3.3 cm The leaflets show evidence of severe acute vegetative endocarditis, there are along the line of closure of the largest cusp four soft nodular masses 1 to 3 mm in diameter, with punctate elevated pink areas about them The edge of the leaflet has attached to it two granular leaf-like appendages from 1 to 2 mm thick and 1.1 cm long, soft in consistency Back of the vegetations are areas of fibrous thickening The other cusp has similar but less well marked lesions Near the posterior attach-

5 Strassmann, P Ueber den Mechanismus des Verschlusses des Ductus Arteriosus (Botalli), Arch f Physiol, 1893, p 566, Anatomische und physiologische Untersuchungen über den Blut Kreislauf beim Neugeborenen, Arch f Gynaek, 1893, xlv, 393



Fig 2—View of the heart from the right and above, showing the probe in in the open ductus (*A*), the vegetations on the pulmonary artery to the left of the probe, the four aortic arch branches, and the two cusps of the pulmonary valve

ment of the anterior cusp is a small ulcerated area 3 mm in diameter. The sinuses of Valsalva are shallower than normal, due to the retraction of the valves. The right coronary artery opens into the aorta by four small orifices. The arteries are otherwise normal. **Aorta.** There are several spots of yellowish discoloration but not of definite elevation or increased density. The aorta has four principal branches, the positions and sizes of which are shown in Figure 2. Circumference of aorta 1 cm above the valve (in formaldehyd hardened specimen) is 6 cm. Circumference of pulmonary artery in corresponding position 6.8 cm. (There is considerable shrinkage in the formaldehyd specimen, but the comparative size of the arteries should be nearly the same, and these measurements show that the pulmonary artery is larger than normal in proportion to the aorta.)

Anatomical Diagnoses—Open ductus arteriosus (Botalli). Anomalies of pulmonary and aortic valves, consisting in the presence of only two segments in each valve. Four primary aortic arch branches. Acute vegetative, and chronic endocarditis, with connective tissue proliferation, of the aortic valve. Vegetations of the ductus Botalli and pulmonary artery. Slight hypertrophy of the right ventricle. Infarcts of both lungs.

Microscopic examination shows an acute endocarditis of the aortic valves, and endarteritis of the aorta, ductus Botalli and pulmonary artery, with vegetations and masses of streptococci.

A section of the ductus stained with Verhoeff's elastic tissue stain demonstrates a large amount of elastic tissue, thus suggesting that deficiency in elastic tissue is not the only factor in producing patency.

COMMENT

This is one of the rare cases of patent ductus Botalli with "typical" signs, and one of the few cases diagnosed during life and confirmed by necropsy. In the series in the accompanying table only one other of the cases of adults had the lesion included in the antemortem diagnosis.

The endocarditis of the aortic valve above seems to indicate that the vegetations about the ductus Botalli and along the pulmonary artery, and also the lung emboli, owe their ultimate origin to this lesion, and that in fact the infection has made a vivid diagram by its lesions of a course of blood from the aorta through the ductus Botalli.⁶ While the embolus which produced the infarction of the lung may have had its immediate origin in the vegetations on the pulmonary artery, it is also possible that it came from the lesions of the aortic valve through the open ductus. The possibility of this form of paradoxical embolism has not received the attention it deserves. It may be nearly as important as the usually cited passages through the foramen ovale, for in 412 cases of congenital cardiac disease patent ductus arteriosus occurred (counting cases with other congenital lesions) 106 times, as compared with 134 cases of open foramen ovale.

⁶ A very similar case of acute aortic endocarditis with extension through the duct is reported by Schlagenhauser. *Ztschr. f. Heilk.*, 1901, xxii, 19.

That the lesion had no great disturbance of function as its sequence is plainly seen by the absence of cardiac symptoms in the case history. Clubbed fingers with slight cyanosis of the nails constitute the only recognized effect. In the heart itself there is slight right ventricular hypertrophy, and on consideration it seems probable that there was a distinct disturbance in the pressure in the pulmonary circuit, the cause for which is of course to be sought in the aortic-pulmonary short circuit, and the result to be seen in the dilated pulmonary artery, and hypertrophied right ventricle, and proved clinically by the palpable and loud pulmonic second sound, which was a striking feature of the heart examination. Very probably the clubbing of the fingers is to be traced to this changed pressure condition.

Were the thrill and murmurs due to the patent ductus Botalli or to the aortic lesion? No fact is conclusive proof one way or the other, but there is an accumulation of probabilities, all of which point in one direction, and which give a basis for a theory very reasonable in appearance. In the first place, why should there be a murmur from the passage of blood through this tube any more than through other branches of the aorta? Of course there is a possibility for the production of a murmur in the interference of the ductus current with the current in the pulmonary artery. Examination of the specimen, however, gives a plainer answer, the ductus comes away from the aorta at a peculiar angle, and at the proximal side of the opening is the sharp ridge described above, an arrangement admirably suited to break up the flow and produce the continuous murmur. Assuming that murmurs are transmitted with the blood flow, this murmur would be heard as in the pulmonary artery. The pathological examination indicated that the aortic lesion was a rather recent one, for there was none of the left ventricular hypertrophy and dilatation of a four years' aortic insufficiency. Clinically, also, the absence of signs of aortic insufficiency at the examination four years before death, and the absence at that time of the cardiac history to be expected in the production of the aortic lesions, point in the same direction. The murmur itself does not correspond to the usual character of an aortic insufficiency murmur, and the continuous humming top thrill would be difficult to explain on that basis. Most probably, then, the continuous thrill and the accompanying murmurs were unconnected with the aortic lesion, but were due to the sharp ridge on the aorta near the orifice of the ductus Botalli. The diastolic murmur, greatest over the aortic area, the systolic thrill at the apex (and perhaps part of the other murmurs) coming at the time other signs of aortic disease were recognized, and at the time when the pathological examination and clinical history indicate aortic disease began, suggests that they were probably due to the aortic lesion.

Case	Age	Sex	Cyanosis	Clubbing	Dyspnea	Heart Examination				
						Right Border	Left Border	Thrill	Murmurs	Other Details
I										
1	26	♀	0	0	0?	Incr	Normal	Felt only once	"Machinery" murmur through whole cycle, loudest in 3d lt space	Dulness in 2 lt space P ₂ +
2	26	♀	0		In crises with palpitation				Presystolic roll at apex	2d sound doubled
3	32	♂	Antemortem	0	Antemortem	Normal	Normal		Short presystolic over precordia	
4	35	♂			Slight					2d sound doubled
5	55	♀	Marked				Normal		Faint systolic at apex	Dulness in 2d space
6	42	♂				Incr	Incr	Suggested at apex	Loud blowing systolic in 2d rt space	P ₂ + Dulness in 2d lt space Severe icterus
7	17	♀	Slight	Present	0	Normal	Normal	Through cycle over pulmonary area	Rough systolic running into diastole over pulmonary area	P ₂ + Dulness and pulsation 2d lt space
II										
8	6½*	♂	Present						0	
9	6*	♀	Attacks	0		Normal	Normal		0	
10	11½*	?	Moderate	Present	On exertion	Incr	Incr	0	Systolic at base antemortem	
11	11½*	♀	0			Incr	Normal		Systolic over pulmonary area	
12	9†	♀	Slight attacks			Incr	Normal	0	Systolic loudest in 2d left space	
13	5†	♀	Marked			Incr	Incr	0	Systolic loudest 5th space 3 cm out	
14	3†	♂	Slight	0		Normal	Normal	0	Rough systolic loudest near apex	P ₂ +
15	7†	♂	Marked		Present	Normal	Normal			
16	6½*	♂	General			Normal	Normal	0	Systolic loudest opposite nipple	Dulness 2d rib to apex
17	17†		Present						0	
18	2†		Present		0	Incr	Normal			P ₂ +
19	2†	♂							0	
20	5†	♀	Present	Present		Normal	Normal		Sawing systolic, loud at base	
III										
19			6		6	Usually Incr		7 — systolic or continuous	Almost always loud systolic or continuous	P ₂ usually —
IV										
34			29%	29%	47%			Systolic over pulm area — 29% Continuous — 59%	Systolic in pulm area — 38% Continuous in pulm area — 59%	P ₂ + in 17 2%

* Weeks

† Months

‡ Days

♀ Female

♂ Male

1 Mead, K C Jour Am Med Assn, 1910, lv, 2205

2 Doufour, H, and Huber Bull et mem Soc med d hôp de Paris, 1911, xxxv, 510

3, 4 and 5 Motzfeldt, K Deutsch, med Wchnschr, 1913, xxxix, 2037

6 Wells, H G Am Jour Med Sc, 1908, cxxvi, 381

7 This paper

8 Weber, I P Proc Roy Soc Sect Study Dis Child, 1908, p. 193

9 Smith, F Proc Roy Soc Sect Study Dis Child, 1908, p. 34

Autopsy

Ductus	Heart, Wt, Gm	Right Ventricle	Left Ventricle	Pulmonary Artery	Valves	Other Organs	Other Defects
Aortic 10 mm pulm 4 mm	395	Dil and hyper	Hyper	dil	Slight mitral and aortic sten		None
4 mm		Hyper	Hyper		Mitral sten and veg		None
8 mm	590	Hyper >	Hyper	dil	Normal		None
2 mm	480	Hyper ~	Hyper	sl, dil	Normal		None
Thrombosed	700	Hyper	Hyper	dil	Normal		None
Aortic 8 mm. pulm 2 mm	300	Slight hyper			Normal	Liver cirrhosis	None
5 mm	252	Slight hyper	0	sl, dil	Aortic veget	Lung infarcts	Two leaflets on aortic and pulmonary valves Four aortic branches
5 mm		Slight hyper	Slight hyper		Normal	Atelectatic patches	None
6x3 mm	95	Slight hyp and dil	Slight				Slight narrowing of aorta, patent foramen ovale and ventricular septum
		Hyper and dil					Aorta rides ventricles, obliterated pulmonary artery, patent ventricular septum
			Hyper	Lumen 1/4 in		Slight emphysema	Aorta rides ventricles, patent ventricular septum, atresia pulmonary artery
				sl, dil		Pneumonia	Absent ventricular septum, slight narrowing aorta, four aortic branches
"Small"							Absent interauricular septum, fused mitral and tricuspid valves, four aortic branches
"Small"		Dil and hyper				Broncho-pneumonia	Large ventricular septum defect, small open foramen ovale
"Mod size"		Hyper		Atresia	Aortic sten	Emphysema	Atresia pulmonary artery, open foramen ovale
	90	Hyper		Atresia dil above	Sl aortic sten	Broncho-pneumonia	Atresia pulmonary artery, open foramen ovale
	.			Atresia			Atresia pulmonary artery
2 mm		Hyper		Oblit	Normal	Atelectasis	Obliterated pulmonary artery
							Aorta and pulmonary artery arise in common
1 mm						Broncho pneumonia	
		Usually hyper	Often hyper	Often dil			
		Hyper in 32 1%	Hyper in 32 1%				

- 11, 12 and 13 Carpenter, G Brit Jour Child Dis, 1908, v, 396
 14 Sawyer I E H Birmingham Med Rev, 1909, lvi, 152
 15 Bach S Arch f Kinderh, 1909, l, 31
 16 Bradley, W N New York Med Jour, 1909, lxxxix, 1302
 17 Vallois, M Bull Soc Obst de Paris, 1910, xiii, 107
 18 Edwards E P Cleveland Med Jour 1911, v, 748
 19 Gerke E Charite Ann 1907, lxxvii, 299
 20 Kinsley, C R Johns Hopkins Hosp Bull., 1911, xlii, 56

Table 1—In the first division of the table are the cases since 1908, of patients over 1 year of age—the youngest happens to be 17, in the second division are the cases since 1908 of under 1 year of age, in the third division are the cases collected by Dr Abbott, and in the fourth those of E H Goodman. The case in this paper is tabulated as Case 7. The table summarizes practically all recorded uncomplicated cases of open ductus Botalli, and a few (occurring since 1908) complicated cases. Notes 1 to 20 are the references to the cases in the order given in the table.

An important point in the physical examination is the mention on June 25 of visible pulsation and dulness in the second left interspace, just after the first sound. This corresponds with the strip of dulness, and the Roentgen-ray shadow so much emphasized by several observers and supposed to be made by the dilated pulmonary artery. Pulsation in the suprasternal notch was noted at the same time.

To compare this with previous cases I shall make use of Dr Abbott's and Dr Goodman's summaries, and my own of the cases published since.

Besides these may be mentioned the case of Dr C H Dunn,⁷ in which an infant with a murmur and slight cyanosis, but no thrill or heart enlargement, was found at necropsy to have an open ductus, and that of Dr A Hayashi,⁸ in which a baby of 10½ months, with normal heart boundaries, a visible pulsation in the fourth, fifth and sixth spaces, a palpable systolic thrill, and a loud systolic and soft diastolic murmur over the precordia, was proved post mortem to have excessive hypertrophy of the left ventricle, active dilatation of the right ventricle, dilated auricles and a ductus Botalli of a 5 mm diameter.

The most interesting single case was reported by Mead. It is Case 1 in the table. Observations covering a period of three years were made. At first slight lateral enlargement in both directions, with a noisy systolic murmur at the base and apex, transmitted to the right of the sternum and almost to the axilla were found. Two years later a strong thrill in the third and fourth right spaces was noted. An examination by Dr Thayer of Johns Hopkins showed a long machinery murmur over the right ventricle, strikingly loud at the base and the first left interspace, with a late accentuation—almost diastolic—high up. The right border was 5.5 cm to the right, the left 8.5 cm. No thrill was felt. An impulse was felt in the second and third spaces. A soft systolic and a soft diastolic murmur were heard at the apex. The pulmonic second sound was loud. The diagnosis was made of septum defect or open ductus arteriosus.

In 1909 paralysis of the right vocal chord was diagnosed.

Roentgen-rays showed a bulge on the left of the heart close to the descending aortic arch, considered to be a hypertrophied and dilated

7 Dunn, C H. Trans Am Pediat Soc, 1913, xxv, 237.

8 Hayashi, A. Monatschr f Kinderh, 1912, xi, 224.

right auricle. The patient then had irregularities and a loud aortic murmur, and died after several attacks of faintness.

At necropsy open ductus arteriosus was found, with a thickened lining and a fold of membrane about it. The heart had three ruptures of the right ventricle. The right ventricle was dilated and hypertrophied, the myocardium degenerated, the pulmonary artery twice the size of the aorta, there was slight aortic and mitral stenosis.

In the analysis of cases in the accompanying table it seems evident that characteristic symptoms or physical signs are rare. Cyanosis occurred in 70 per cent of the cases as against the 31 per cent of Dr Abbott, and was about as frequent in the uncomplicated cases as in the whole. Clubbing of the fingers was noted in only 15 per cent, in 25 per cent of the cases there was dyspnea, as against Dr Abbott's 31.5 per cent. A constant definite thrill was noted only once, Dr Abbott finds it in 37 per cent, and many writers (De la Camp⁹ and others) speak of it as one of the most useful diagnostic signs. A systolic murmur over the base, extending into diastole, was noted only twice (both of them cases of adults). A systolic murmur, loudest over the base, was present in five other cases (only one of them a case of an adult). Dr Abbott, however, finds that a peculiar loud murmur is nearly always produced, almost invariably beginning in systole, and localized near the base of the heart. A murmur of some kind was present in 65 per cent of the cases above.

Goodmann, in his collection of 34 cases with necropsy, found twenty females and eleven males. Cyanosis was found in 29 per cent, dyspnea in 47 per cent, palpitation in 37 per cent, clubbed fingers in 29 per cent, pulsation in the second left interspace in 59 per cent, a systolic thrill over the pulmonary area in 29.4 per cent, a systolic and diastolic thrill over the same area in 59 per cent, a systolic murmur over the area in 38 per cent, and continuous murmur in 59 per cent. The pulmonic second sound was accentuated in 17.2 per cent. The left ventricle was hypertrophied as often as the right—32.1 per cent.

In this series, whether analyzed by classifying the cases according to the division into simple and complicated cases, or into infantile and adult, the sexes are as evenly divided as possible. Dr Wells, in his forty-one cases, found a remarkable preponderance of females (63 per cent), which in the light of this series now seems probably was a matter of chance.

Evidently none of the symptoms or signs just discussed are to be depended upon for a constant diagnosis.

⁹ De La Camp. Familiäres Vorkommen Angeborener Herzfehler — Zugleich ein Beitrag zur Diagnose der Persistenz des Ductus Arteriosus Botalli, *Berlin. Wchnschr.*, 1903, 21, 48.

The pathological finding of hypertrophy with or without dilatation of the right ventricle was noted in all of the adult cases and in seven of the infantile. Dr. Abbott states that it is the usual pathological finding. Dilatation of the pulmonary artery was found in five of the adult cases and one of the infantile, and clinically the dulness in the second interspace near the sternum emphasized as its result was actually observed four times in the adult cases. (Of course in these statistics it must be remembered that in the infantile cases the examination was evidently often far from thorough.) The pulmonic second sound was noted to be exaggerated in three of the adult cases. It is evident, then, that clinical signs depending on an increased pressure in the pulmonary circuit are the most constant signs in this series. They are common to so many other conditions, however, dilatation of the pulmonary artery often occurring in congenital lesions such as defects of the lower part of the interauricular septum, widely patent foramen ovale, defects of the base of the interventricular septum, transposition of the arterial trunks, stenosis of the aorta, and without other defects, that they do not seem to be of great diagnostic importance.

This analysis indicates that in a large number of cases there is nothing in the way of signs or symptoms to make us sure of an open ductus arteriosus, or even to make us suspect it. Hochsinger emphasizes the difficulty of diagnosis in infants, but hardly in adults. Before a conclusion based on such a small number of cases is accepted, however, it should be determined whether it is supported by reason. What should we expect as the clinical result of the lesion? It does not seem to me that a murmur or thrill is by any means a necessary or even likely result from the slight intermixture of currents arising from the presence of an additional aortic branch at an acute angle, emptying by a small opening into the pulmonary artery. (Hochsinger makes this mixing of currents his main explanation of the origin of the murmur, but there are no facts to support this view except the lack of a murmur in certain cases in which such mixing would not be expected. He has too few cases, however, and murmurs are lacking too often, to allow his arguments to convince.) It is interesting to observe that in the three adult cases in which a thrill or murmur at the base of the heart was noted, there was a distinct fold of endocardium about the aortic orifice of the duct (see description of the pathological findings in this and in Mead's case), and in one case a mound-like elevation about the pulmonary orifice (Wells' case). It seems much more reasonable to consider that the murmur or thrill is not the result of the patency alone, but depends on the presence in addition of some endocardial projection, or other roughening or vegetation, such as is recognized in other situations to give rise to

murmurs This especially, when it is considered that in the cases with necropsy the ductus was open to almost a constant diameter, thus giving each time about the same anatomical reason for a murmur The clinical findings of absent murmurs in many cases is in perfect accord with this reasoning The conditions due to increased pressure in the pulmonary circuit could hardly be expected to be very marked when the small size of the ductus is considered (barely over 5 mm), and there is of course nothing pathognomonic about them when discovered Combinations of the signs discussed can be effected by combinations of lesions, which are often found in congenital heart disease No signs are necessarily present when the ductus is open, then, which are sufficiently specific to afford us means of diagnosis Even the peculiar murmur occasionally produced accessorially may be closely simulated in pulmonary stenosis, or in defects of the ventricular septum In occasional cases the peculiar humming systolic murmur, loudest over the pulmonary area, with or without a thrill, combined with signs of increased pressure in the pulmonary artery, such as loud and palpable pulmonic second sound, increased dulness in the second left interspace, increased in the middle Roentgen-ray shadow, and suprasternal pulsation, with or without cyanosis, clubbed fingers, and dyspnea, justify the inclusion of "open ductus" in the differential diagnosis Of course a continuous murmur over the pulmonary area makes a more certain diagnosis possible The indefinite murmurs, etc., often present, may give rise to confusion with acquired valvular lesions in a way which can easily be seen from the tabulated cases The present series of cases brings out the rarity of recognizable symptoms, especially of the thrill and characteristic murmur, rather than new symptoms or signs

Many articles have been published (Arnheim,¹⁰ De La Camp,⁹ Miller,¹¹ Wessler and Bass¹²) in which it is assumed or claimed that the diagnosis can be made frequently, or almost always, by using the Roentgen-ray and careful percussion to determine the dilatation of the pulmonary artery It is noteworthy, however, that most of these articles are based on cases without necropsy

In the cases since 1908 there are only two with roentgenoscopy showing a dilated pulmonary artery confirmed by necropsy, no necropsy was made in the three Roentgen-rayed cases of Dr Abbott In view of these facts and of the non-characteristic nature of the findings, any emphasis on this method for diagnosis seems unwarranted

10 Arnheim, G Persistenz des Ductus Botalli, Berl klin Wchnschr, 1903, xl, 616

11 Miller, R, and Orton, G H A Case of Open Ductus Botalli with X-Ray Examination, Brit Jour Child Dis, 1913, x, 109

12 Wessler and Bass Persistent Ductus Botalli and Its Diagnosis by the Orthodiagraph, Am Jour Med Sc, 1913, clxv, 543

In regard to the prognosis, the table brings out strongly the apparent fact that the patients that die in infancy are those with other congenital heart lesions, while those that live over one year, have an indefinite term of life. It will be noted that none of the adult patients had another important congenital heart lesion, while of the patients that died under 1 year of age only two failed to have one. The pure cases of open ductus, in other words, have little interference with function.

In spite of all that has been written on the subject, conclusions must be tentative until the extraordinarily small number of cases carefully and thoroughly observed is much increased.

SUMMARY AND TENTATIVE CONCLUSIONS

1 The case presented here is one of the rare cases with those signs of open ductus arteriosus usually regarded as typical.

2 It is one of the rare cases diagnosed during life and confirmed by necropsy.

3 The case illustrates the actual course of blood during life through the ductus.

4 The possibility of a practically unrecognized form of paradoxical embolism is shown.

5 A summary and discussion of cases seems to show that

(a) The physical signs formerly regarded as characteristic are more often absent than present, and the possibility of diagnosis must be rare.

(b) Most of the signs discussed are really not absolutely characteristic.

(c) Combinations of the signs can occur in combinations of other lesions.

(d) When there is the rare combination of signs formerly regarded as diagnostic, the presence of the lesion is probable, but not certain.

(e) Far too few cases have had roentgenoscopy and necropsy to determine the value of the Roentgen-rays for diagnosis.

(f) The Roentgen rays determine only a dilatation of the pulmonary artery, which is present in several other lesions than open ductus, so that the Roentgen ray findings will not make a certain diagnosis possible.

(g) The characteristic murmur is probably not the result of the patency of the duct alone, but requires in addition the presence of endocardial folds, vegetations or other roughenings, about the ductus.

- (h) The only result of the patency is increased pressure in the pulmonary artery (with its secondary effects)
- (i) The former view of preponderance of cases in females was merely the result of chance
- (j) The open ductus alone does not lead to early death, but when complicated with other congenital heart lesions death is usual within one year
- (k) Very few cases have been carefully observed and recorded
More cases are needed before conclusions can be definite

I wish to express my thanks to Dr Henry A Christian, chief of the medical service, for his permission to report the case, and to Dr W T Councilman, for valuable suggestions in the treatment

In addition to the references mentioned in the text, the following may be consulted

Zinn, W Zur Diagnose der Persistenz des Ductus Arteriosus Botalli, Berl klin Wchnschr, 1898, xxxv, 433

THE CLINICAL ACTIONS OF VERATRUM *

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Veratrum is obtained chiefly from the rhizome and roots of *Veratrum viride*, an American plant, although the *Veratrum album*, a European plant, has also been used in medicine. Both varieties contain a mixture of alkaloids, the main action being due to protoveratrin. In the past, veratrum has been employed mainly as a cardiac depressant and to soften the pulse and lower the blood pressure in eclampsia.

According to Wood¹ the effects of therapeutic doses on the circulation of mammals (dog and rabbit) consist of a slowing of the pulse and a moderate fall in blood pressure, the effects being rather persistent. The slowing is due mainly to stimulation of the vagus center (abolished by cutting the vagi). The vasomotor center is not stimulated except by the fall in blood pressure and by respiratory embarrassment.

Toxic doses produce at first exaggeration of the vagus stimulation as a marked slowing, irregularity and final arrest, with corresponding fall in blood pressure. This is followed by sudden extreme acceleration and rise of blood pressure (partly asphyxial and partly spasmodic). This rise may last for several minutes, and is succeeded by a rapid progressive fall and death. Other signs of "toxicity" are profuse sweating, nausea, followed quickly by vomiting, diarrhea, dysphagia, collapse, paralysis and light convulsions.

The object of the present study was to ascertain more definitely the effects produced by veratrum in normal and diseased human individuals, with special reference to the circulatory system. Many of the studies reported in the literature lack definite objective data, and whatever data exist need the confirmation of the improved and more modern methods of observation. Then, too, veratrum being a very active drug pharmacologically, there is reason to believe that certain hitherto overlooked therapeutic applications could be made of it. A report of the results thus far obtained is here presented.

* Submitted for publication March 12, 1915

* From the Pharmacological Laboratory, Medical School, Western Reserve University, and the Medical Services of the Lakeside and City Hospitals

1 Wood, H. C., Jr. Jour. Am. Med. Assn., 1906, xlvii, 2061

METHODS

The patients were selected from the wards of Lakeside and City hospitals. All were convalescent with the exception of Patients 4 and 8. During the observations all patients were lying in bed while the pulse rate and blood pressure were taken. The noon day meal consisted of a soft diet.

The pulse was taken for half a minute at the time of the first dose of veratrum and at intervals of fifteen to thirty minutes until the effects of the drug were pronounced. The blood pressure was taken by the auscultatory method before the administration of the drug and again when the pulse rate had reached a minimum. The patient (Case 6) was allowed to walk around for five minutes when the pulse reached 60 with no effect on the rate.

The preparation used was the 10 per cent tincture from *Veratrum album*². Each dose was given in seven cases with from one to three glasses of water. By mistake one patient (Case 4) received only an equivalent of one-fourth glass and complained that each dose caused considerable gastric irritation, of which none of the others complained. All patients noted a fulness and throbbing in the head when the pulse rate reached its minimum.

PROTOCOLS OF CASES

The following abbreviated protocols contain the essential data obtained with eight patients.

CASE 1—Convalescent from acute nephritis. Pulse rate for ten days previously ranged from 80 to 100 per minute. Blood pressure on three preceding days at the same time each day was 135 mm systolic, 95 mm diastolic. Total dosage of *veratrum album* was 60 minims in three hours. Pulse rate at administration of first dose was 102, systolic blood pressure, 135 mm, diastolic, 95. One hour following the last dose pulse rate was 63, systolic blood pressure, 92 mm and diastolic, 60 mm. Thirty minutes later the patient became nauseated and vomited.

CASE 2—Convalescent from typhoid fever, received a dosage of 20 minims in one hour with no appreciable effect on the pulse rate and blood pressure.

CASE 3—Convalescent from acute nephritis. Pulse rate for ten preceding days was 66 to 90. Systolic blood pressure had varied from 180 mm to 190, diastolic, from 125 mm to 135 mm. At time of first dose pulse rate was 87, systolic blood pressure, 190 mm, and diastolic, 135 mm. Total dose of veratrum was 60 minims. Fifty minutes following the last dose pulse rate was 63, systolic blood pressure, 135 mm, and diastolic, 95 mm. Twenty minutes later patient became nauseated and vomited.

CASE 4—Hypertonus. As this was the patient's first day in the hospital, no former data could be obtained. Pulse rate at time of first dose was 88, systolic blood pressure, 228 mm and diastolic, 142 mm. One hour and fifteen minutes after the last dose, pulse rate was 63, systolic blood pressure, 160 mm and diastolic, 130 mm. Thirty minutes later patient became nauseated and vomited.

² I wish to express my thanks to Prof. Henry Kraemer of the Philadelphia College of Pharmacy, who furnished us with several preparations of different species of veratrum.

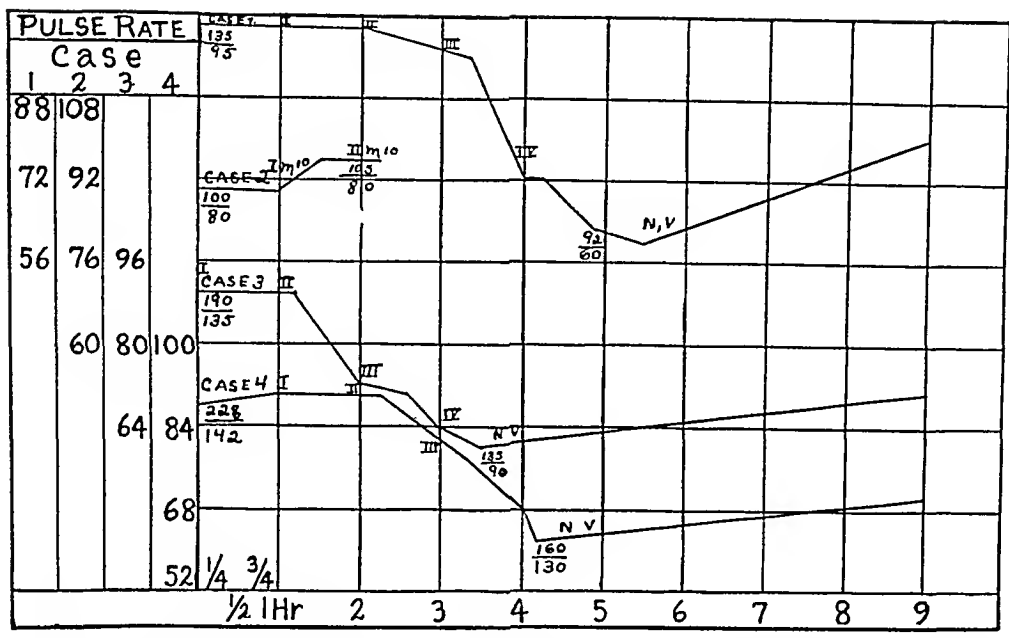


Fig 1—Effect of veratrum on pulse rate and blood pressure (individual cases) In the fractions the numerator refers to systolic blood pressure, the denominator to diastolic pressure "H" means headache, "N" nausea, "V" vomiting The number of the dose is indicated by Roman numerals Each dose represents 15 minims of tincture of veratrum, except as indicated by Arabic numerals These data apply also to Chart 2

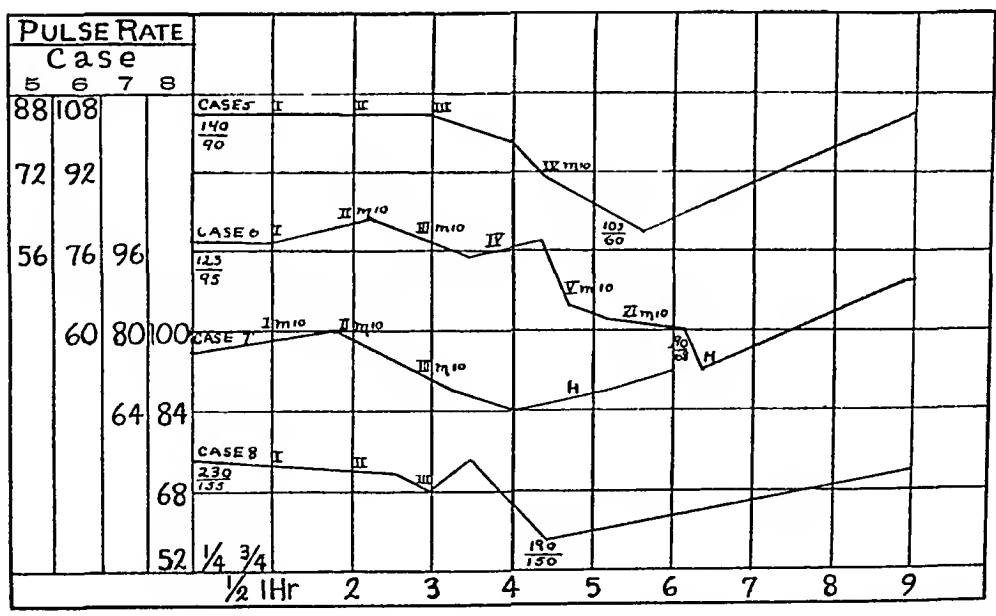


Fig 2—Effect of veratrum on pulse rate and blood pressure (individual cases) See legend Chart 1 for additional data

CASE 5—Convalescent from typhoid fever Pulse rate on five days previous was 72 to 100 Pulse rate at the time of the first dose was 84, systolic blood pressure 140 mm and diastolic, 90 mm Total dose of veratrum was 55 minims in three hours and twenty minutes One hour and fifteen minutes after the last dose, pulse rate was 60, systolic blood pressure 105 mm and diastolic 60 mm , no toxic symptoms

CASE 6—Convalescent from acute nephritis Pulse rate for ten preceding days ranged from 80 to 90 Pulse rate at the time of the first dose was 78, systolic blood pressure 125 mm and diastolic 95 mm Received 75 minims of veratrum in four hours and five minutes Pulse rate fifty-eight minutes following the last dose was 52, systolic blood pressure 90 mm and diastolic 68 mm The toxic symptoms were only slight nausea and headache

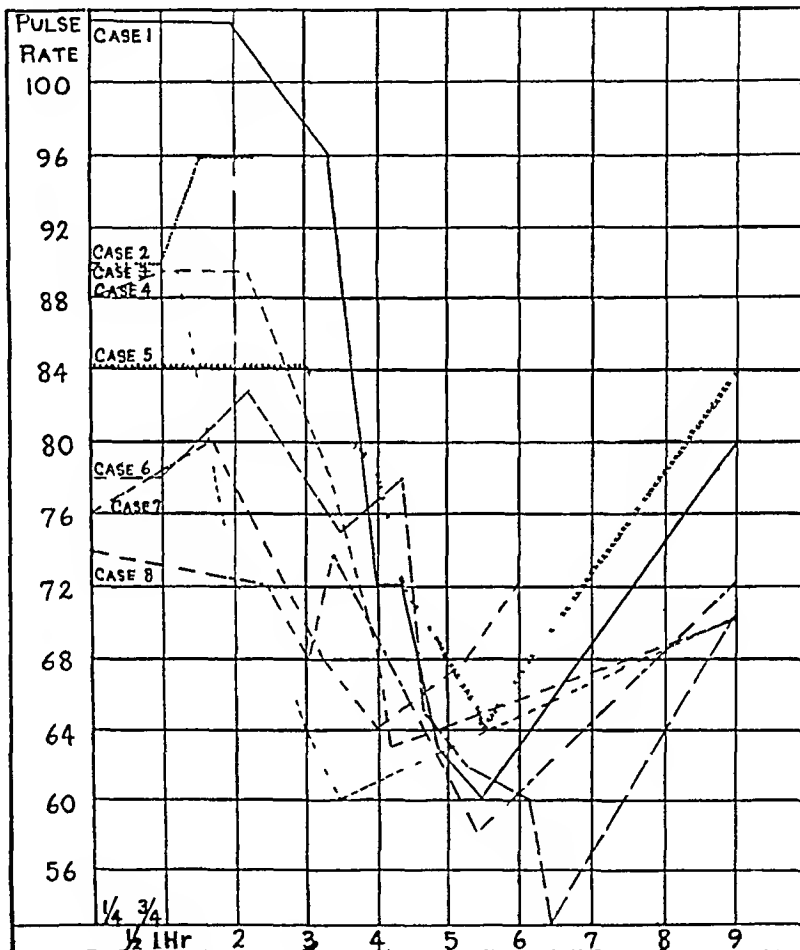


Fig 3—Effect of veratrum on pulse rate (composite curve from all cases)

CASE 7—Tuberculosis of lung, no previous data obtained At the beginning of observation pulse rate 76 Pulse rate forty-five minutes following the last dose was 64

CASE 8—Hypertonus and syphilitic aortitis Pulse rate for ten days previous was 68 to 96, blood pressure had been taken almost daily for a week previously, and ranged from 265 mm to 230 mm, systolic, 175 mm to 150 mm, diastolic Nitrites in the form of nitroglycerin reduced the systolic blood pressure from 265 mm to 230 mm , the diastolic from 175 mm to 150 mm Total dose of veratrum given was 45 minims during a period of two hours One-half hour after the last dose, pulse rate was 58, systolic blood pressure 190 mm and diastolic 150 mm , no toxic symptoms

The data from these cases are graphically presented in Figures 1 and 2, and in the form of a composite curve in Figure 3. These indicate that in those patients receiving enough of the drug, that is, from 30 to 75 minims of the tincture, an average fall in pulse rate of 26.9 beats resulted. In all these cases the rate was lowered independent of the original rate. Since three cases of acute nephritis and one case of typhoid were convalescent, and there were, in addition, two cases of hypertonus, a division into two groups will be made. In Group 1, the convalescent cases, the average fall of systolic blood pressure was 39.5 mm, of the diastolic, 31.75 mm. In Group 2, hypertonus cases, the average systolic fall was 49 mm, diastolic 8.5 mm. Three cases presented "toxic" symptoms consisting of nausea and vomiting, but in each of these cases the fall in pulse rate and blood pressure preceded the "toxic" symptoms. It has as yet been impossible to determine definitely the duration of action of veratrum in the doses given, although the hospital charts indicate a recovery of from ten to fifteen beats per minute in six hours following the last dose.

SUMMARY

1 The therapeutically effective dose of the tincture of *Veratrum album* for adults ranges from 30 to 75 minims.

2 Clinically, the effects of veratrum resemble the pharmacologic effects, and consist of a slowing of the pulse rate amounting to 12 to 42 beats per minute, and a fall of systolic blood pressure amounting to about 39, of the diastolic, 32 mm. The two hypertonus cases showed a fall of systolic blood pressure amounting to about 49 mm, of the diastolic about 8 mm.

3 The circulatory effects produced by veratrum take place independently of the "toxic" symptoms, such as nausea and vomiting.

I wish to express my thanks to Prof. Sollmann and Dr. Hanzlik for numerous suggestions and guidance in the work and criticism of the manuscript, to Professors Hoover and Carter for permission to use the material of their clinics at Lakeside and City Hospitals, respectively.

THE RELATION OF CALCIUM TO THE DELAYED COAGULATION OF BLOOD IN OBSTRUCTIVE JAUNDICE¹

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It has long been recognized that in certain cases of obstructive jaundice there is a tendency to hemorrhage due to the delayed coagulation of the blood. Morawitz and Bierich¹ studied the causes of bleeding in cholemia and came to the conclusion that the altered coagulation time in these cases could be traced to delayed formation of fibrin ferment. They attributed this delay to a diminution or absence of thrombokinase. They believed that the altered coagulation time was not due to the presence of cholates or biliary acids in the blood and was independent of the duration or intensity of the jaundice. Kunika² investigated the clinical value of the determination of the coagulation time in cases of icterus and concluded that the delay was due to a decrease in the liver function. King and Stewart,³ in the course of an investigation of the cause of bradycardia and low blood pressure in dogs with obstructive jaundice, found that the calcium content of the blood was increased and suggested that in icteric conditions the calcium might be combined with bilirubin and biliverdin as a protective mechanism against the toxic effect of these bile pigments. King, Bigelow and Pearce⁴ found that the calcium output was increased in obstructive jaundice in dogs. They found an increase in the calcium content of the blood, liver and kidneys. The excess of calcium which appeared in the stools was accompanied by a decrease in the calcium of the other tissues. They did not attempt to study the coagulation in these cases but made the suggestion that the retarded coagulation time may be due to the fact that the calcium is bound to the biliary pigments in such a way as not to be promptly available for the process of clotting.

In a previous article⁵ we have studied the processes of coagulation in normal human blood. We have now applied the methods of investigation followed in those studies to the examination of the blood in various types of delayed coagulation, among them the retarded coagulation associated with obstructive jaundice. Our experience coincides

*Submitted for publication, March 9, 1915

1 Morawitz and Bierich. Arch f exper Path u Pharmacol, 1907, lvi, 115

2 Kunika, S. Deutsch Ztschr f Chir, 1912, cxviii, 574

3 King and Stewart. Jour Exper Med, 1909 xi, 673

4 King, Bigelow and Pearce. Jour Exper Med, 1911, xiv, 159

5 Lee, Roger I, and Vincent, Beth. The Coagulation of Normal Human Blood, THE ARCHIVES INT MED, 1914, xiii, 398

with that of other observers that the coagulation time is not markedly altered in the group of cases called catarrhal jaundice. In this paper we shall limit the discussion to obstructive jaundice without apparent disturbance of liver function. Those cases of liver disease with non-obstructive jaundice present a marked interference with the coagulation of the blood. But according to our present views the reasons for a delay in coagulation in such cases is not the same as in obstructive jaundice with a functioning liver.

The data presented are both clinical and experimental.

CLINICAL OBSERVATIONS

The clinical data were obtained from cases of obstructive jaundice observed in the wards of the Massachusetts General Hospital. A considerable group of cases was studied rather incompletely. Five cases were studied more in detail. It was our experience that there was little or no change in the coagulation time of the blood when taken by the method described by Lee and White,⁶ until after the jaundice had been noticed by the patients for periods averaging five weeks. Case 3 of the series will be given in some detail as it is fairly typical of the rest and presents the necessary points for discussion.

CASE 3—Hospital No 196,455. A man, aged 53, came under observation July 8, 1914. Family and past history, negative. For four weeks the patient has noticed increasing jaundice and weakness, and has lost 12 pounds. There are no other symptoms.

On examination, considerable loss of weight is noted, the skin and sclera are deeply jaundiced, there are small petechial spots on the legs. Chest negative. Liver dullness extends from the fifth rib to 4 cm below the costal margin where an indistinct edge is felt. Below this edge is felt a rounded mass, taken to be the gallbladder. Examination otherwise negative. Urine negative except for bile. Wassermann negative. The stool was the typical soapy stool with increased fatty acids, but no bile by Hammarsten's test. Gastric examination negative by Ewald test meal and bismuth roentgenogram. On July 10, the coagulation time was seven and a half minutes, which was interpreted as being within the upper limits of normal for that method. On July 18, coagulation time was ten and a half minutes, which was interpreted as being abnormal. For four days he was given calcium lactate 60 grains a day and bilisalol 9 grains a day. On July 24, the coagulation time was eight minutes. Without treatment the coagulation time of the blood became retarded, until July 31, when the time was fifteen minutes. At this time some blood was taken in oxalate and studied according to the methods described in our previous paper.

As a result of this examination it was apparent that cytozyme, serozyme and fibrinogen were present in the patient's blood and active to a normal degree. These points will be discussed more in detail later. There was evidence of a lack of available calcium. This lack of available calcium was then studied in two ways.

1. By contrasting the coagulation time of 1 c.c. of blood taken in the usual way with the coagulation time of the same amount of blood placed in a similar small glass tube to which had previously been added a certain amount

⁶ Lee and White. *Am Jour Med Sc*, 1913, cxlv, 495.

of calcium The amount of calcium which we used arbitrarily was 3 drops of a 1 per cent solution of calcium chlorid Control determinations, on normal bloods and on bloods showing a delayed coagulation time due to other causes than obstructive jaundice, showed that the introduction of this amount of calcium made no difference in the controls In the obstructive jaundice cases, however, there was usually a striking change

2 The therapeutic administration of calcium, and the subsequent determination of the coagulation time

In Case 3 on August 1, 1 c c of blood clotted by the usual method in thirteen minutes, but in the tube with 3 drops of the 1 per cent calcium chlorid it clotted in five minutes, which is within the normal limits On August 1 the administration of 100 grains of calcium lactate per day was begun by mouth As was our experience in the other cases in this series it was several days before there was any marked change in the coagulation time of the blood

On August 6 the coagulation time was ten minutes under the usual conditions and five minutes in the tube with the calcium On August 9, however, the coagulation time was seven minutes under the usual conditions and five minutes in the tube with the calcium The patient was then considered to be in a condition which warranted operation as regards the danger from hemorrhage

At operation on August 10 there was no abnormal bleeding although there was an extensive resection of a mass in the common duct which microscopic examination showed to be adenocarcinoma The patient died of shock and pneumonia in forty-eight hours with no evidence of hemorrhage There was no necropsy

The striking facts from the clinical data of this series were the following

1 The relatively long time after the onset of jaundice before delay in coagulation, averaging five weeks This probably depends not only on the intensity of the jaundice but also on the amount of calcium in the other tissues which is gradually taken into the blood in the course of five weeks, as King, Bigelow and Pearce have shown

2 The striking parallelism between the determinations of the coagulation time of the blood and the tendency to hemorrhage especially as seen at the time of operation

3 The value of the simple control determination of the coagulation time by the use of a second determination with 3 drops of calcium chlorid 1 per cent to 1 c c of blood This test has been constant and seems to determine the indication for the use of calcium therapeutically We have called the procedure the "calcium in vitro" test

4 The apparent necessity for the administration of large doses of calcium by mouth over a period of several days before the coagulation time shows any marked change This conclusion is based on many observations and many attempts to vary the coagulation time

LABORATORY OBSERVATIONS

Laboratory experiments were carried out with the blood of the patients in this series By means of a syringe 18 c c of blood were taken from the arm vein directly into 2 c c of 1 per cent oxalate

Normal blood was taken in a similar fashion as a control. These bloods were put through various tests described in our previous paper. The blood platelets were isolated and found to act normally in the pathological blood, both in hastening the clotting of blood, the formation of thrombin and the retraction of the clot. Serozyme was obtained and found to be efficient in the production of thrombin. The test used for fibrinogen was merely the observation of the firmness of the clot. There seemed to be no difference between the clots of the pathological plasmas and those of the normal controls. The only discrepancy found was in the optimum amount of calcium required to recalcify the oxalated plasma. A typical protocol follows.

The oxalated blood of the patient in Case 3 and a control normal blood were centrifuged at low speed for ten minutes. The control (so-called "cloudy plasma"), on being recalcified with 4 volumes of the recalcifying fluid, clotted in nine minutes. The plasma from the patient in Case 3 clotted in twenty-two minutes. An increase in the amount of calcium in the recalcifying fluid did not appreciably change the clotting time of the cloudy plasma in the normal case but it markedly shortened the clotting time of the pathological blood. The plasma in Case 3 plus 4 parts of the recalcifying fluid clotted in twenty-two minutes. With the addition of 1 drop of 1 per cent calcium chlorid solution it clotted in seven minutes, 1 cc of normal plasma plus 4 parts of the recalcifying fluid clotted in nine minutes. By the addition of 1 to 3 drops of 1 per cent calcium chlorid solution it clotted in seven minutes.

To cause clotting in some of our cases of obstructive jaundice with a delayed coagulation time, required seven volumes of the recalcifying fluid instead of the normal, which is four. (Four volumes of the recalcifying solution contain one and one-half times the calcium needed to neutralize the oxalate in one volume of the plasma solution, oxalated 1:1,000.)

In order to confirm our laboratory findings, bile was added directly to normal plasma. This bile was obtained from two sources: one, the ordinary powdered ox bile of commerce, taken up with 16 parts of salt solution, the other, sterile bile obtained from a human gallbladder at the time of operation. This bile was diluted 1:4 with salt solution.

The following protocol is typical of many experiments.

Normal "cloudy plasma" plus 4 volumes of the recalcifying fluid clots in sixteen minutes. Four drops of normal plasma, plus 1 drop of bile, plus 4 or 5 volumes of the recalcifying fluid does not clot. Four drops of normal plasma, plus 1 drop of bile, plus 6 volumes of the recalcifying fluid, clots in seventy minutes. If the calcium be gradually increased, clotting can be obtained in twenty minutes. Now if 2 drops of bile be added it requires double the amount of calcium to obtain even feeble clotting. By the addition of an excess of calcium, clotting can be obtained in twenty-four minutes. On the other hand, the clotting time of the recalcified oxalated plasma without bile is not hastened by an increase in the amount of calcium and is delayed when the calcium is in great excess. Four drops of oxalated plasma plus 16 drops of the recalcifying fluid, clots in seventeen minutes, plus 2 drops of 1 per cent calcium chlorid, in sixteen minutes, plus 4 drops, in twenty-two minutes, plus 10 drops of calcium

chlorid, in thirty-two minutes. If an excess of bile be added there is no clotting no matter how much calcium is added. If the unit be taken as 4 drops of the oxalated plasma, which normally clots on the addition of 4 volumes of the recalcifying fluid in about sixteen minutes, the addition of 3 drops of ox bile in normal salt solution 1:16, or diluted human bile, 1:4, is sufficient to prevent clotting despite the presence of any amount of calcium.

Furthermore, it was found that the effect of weak solutions of bile added after the formation of thrombin could apparently be neutralized by the calcium, but when the bile was present in a considerable amount, an active thrombin would not clot a fibrinogen solution no matter how much calcium was used.

We also attempted to determine whether the action of the bile could be neutralized by cytozyme or serozyme but no results were obtained. An excess of calcium seemed to counteract the effect of bile in weak solutions. On the other hand, in strong solutions, the addition of calcium did not counteract the effect of bile. The action in vitro of a solution of ox bile in normal salt solution was very similar to that of human bile obtained from a gallbladder. It seems probable that the amount of bile in the blood corresponds closely to the mixture of plasma with a weak solution of bile.

EXPERIMENTAL OBSTRUCTIVE JAUNDICE

A condition of obstructive jaundice was produced experimentally in a dog. Repeated observations were made on the coagulation time, when the coagulation time showed definite retardation the therapeutic effect of calcium both by mouth and intravenously was tested. The details of the experiment were the following:

A female dog weighing 5,000 gm, was operated on under ether anesthesia on Sept 13, 1914. The common bile duct was doubly ligated and 0.5 cm. of the duct resected between the ligatures. A complete obstructive jaundice resulted and persisted until the end of the experiment. At the end of twenty-four hours the urine showed bile, after forty-eight hours the stools became light colored and repeated examination showed the absence of bile by Hammarsten's test. The coagulation time was determined before operation. One c.c. of blood plus 3 drops of sodium chlorid solution clotted in three minutes, 1 c.c. of blood plus 3 drops of 1 per cent calcium chlorid clotted in three minutes.

On September 27, two weeks after operation, the coagulation time of blood taken from the jugular vein was as follows: 1 c.c. of blood, plus 3 drops of sodium chlorid solution, clotted in six and a half minutes, 1 c.c. of blood, plus 3 drops of 1 per cent calcium chlorid solution, clotted in six and a half minutes.

On October 23, six weeks after operation, the dog had lost considerable weight but was lively and seemed well. Weight 4,200 gm. Coagulation time—jugular vein—1 c.c. of blood, plus 3 drops sodium chlorid solution, clotted in nine minutes, 1 c.c. of blood, plus 3 drops of 1 per cent calcium chlorid solution, clotted in four minutes.

October 25, coagulation time—jugular vein—1 c.c. of blood, plus 3 drops of sodium chlorid solution, clotted in twelve minutes, 1 c.c. of blood, plus 1 drop of 1 per cent calcium chlorid solution, clotted in twelve minutes, 1 c.c. of blood, plus 3 drops of 1 per cent calcium chlorid solution, clotted in four minutes,

1 cc of blood, plus 5 drops of 1 per cent calcium chlorid solution, clotted in three and a half minutes. At 1 30 p m the dog was given, intravenously, 20 cc of calcium lactate, 2 per cent, in sterile salt solution. There was no apparent effect. One hour later, coagulation time, jugular vein 1 cc of blood, plus 3 drops sodium chlorid solution, clotted in four minutes, 1 cc of blood, plus 1 drop of 1 per cent calcium chlorid solution, clotted in seven minutes, 1 cc of blood, plus 3 drops of 1 per cent calcium chlorid solution, clotted in seven minutes, 1 cc of blood, plus 5 drops of 1 per cent calcium chlorid solution, clotted in seven minutes.

On October 26, coagulation time—jugular vein—was as follows 1 cc of blood, plus 3 drops of sodium chlorid solution, clotted in six minutes, 1 cc of blood, plus 3 drops of 1 per cent calcium chlorid solution, clotted in five minutes.

On October 27, the coagulation time—jugular vein 1 cc of blood, plus 3 drops of sodium chlorid solution, clotted in eight and a half minutes, 1 cc of blood, plus 3 drops of 1 per cent calcium chlorid solution, clotted in five minutes. At 12 30 p m the animal was given, intravenously, 15 cc of a 2 per cent calcium lactate solution in normal salt. The coagulation time—jugular vein—one hour later, was as follows 1 cc of blood, plus 3 drops of sodium chlorid solution, clotted in seven minutes, 1 cc of blood plus 3 drops of calcium chlorid, 1 per cent, clotted in five minutes.

On October 28, coagulation time of blood 1 cc of blood, plus 3 drops of sodium chlorid solution, clotted in twelve minutes, 1 cc of blood, plus three drops of 1 per cent calcium chlorid, clotted in seven minutes.

On October 29, coagulation time—jugular vein 1 cc of blood, plus 3 drops of sodium chlorid solution, clotted in eleven minutes, 1 cc of blood, plus 3 drops of 1 per cent calcium chlorid solution, clotted in five minutes. At 10 a m, 35 cc of a 2 per cent calcium lactate solution in normal salt was given intravenously. The coagulation time—jugular vein—one and a half hours later, was 1 cc of blood, plus 3 drops of sodium chlorid solution, clotted in nine minutes, 1 cc of blood plus 3 drops of 1 per cent calcium chlorid solution, clotted in five and a half minutes.

The dog was then given calcium lactate by mouth in capsules to the amount of 50 grains a day for three days. At the end of that time, the coagulation time—jugular vein—was as follows 1 cc of blood, plus 3 drops of sodium chlorid solution, clotted in six and a half minutes, 1 cc of blood, plus 3 drops of 1 per cent calcium chlorid solution, clotted in seven minutes. The next day the animal was found dead in the cage. Necropsy at 2 p m, in brief, showed a thin dog with bile-stained tissues. There was no evidence of hemorrhage, the peritoneal cavity contained 250 cc of cloudy fluid. The peritoneum was lightly injected with occasional flakes of fibrin. Over the liver was considerable shaggy fibrin. Numerous small abscesses were found in the liver. The common bile duct was found permanently interrupted. On opening the proximal end of the duct purulent material and bile were found. The heart cavities were filled with a firm post-mortem clot. The organs were macroscopically negative except for the staining with bile. Microscopical examination was negative. Culture from the heart showed a few colonies of staphylococcus albus, culture from the liver abscesses showed a scum growth of staphylococcus albus.

It is perhaps unfortunate that the picture was complicated by the low grade of sepsis, but we doubt if this sepsis affected the results in the slightest degree.

In general the results in this experiment correspond closely with our clinical experience. In both conditions obstructive jaundice resulted in a delay in the coagulation time of the blood. This delay, even when the obstruction was complete, was not apparent immediately but gradually increased with the persistence of the jaundice and seemed

to reach its maximum only after about five weeks. It was evident that, experimentally, clinically, and in vitro, this delay in coagulation could be counteracted to a large extent by calcium. In the dog and in human beings the administration of calcium by mouth in sufficient quantity seemed effective. In the dog calcium given intravenously had a very prompt but rather temporary effect on the coagulation.

SUMMARY AND CONCLUSIONS

Obstructive jaundice in the presence of a liver functioning in an adequate manner causes a delay in the coagulation time of the blood. This condition must be differentiated from certain somewhat similar conditions in which the liver itself is seriously damaged. The delay in the coagulation of the blood in obstructive jaundice is apparently due to a lack of available calcium in the blood and can be counteracted by the administration by mouth of calcium salts. Other workers have demonstrated an increase of calcium in the blood in obstructive jaundice and have suggested the plausible explanation that the bile pigments in the blood form a more or less loose union with the calcium salts and so render the calcium unavailable for immediate use in the process of coagulation. Our clinical experience shows that the need of more calcium can be very simply demonstrated at the bedside by the "calcium in vitro" test which we have described.

The results of our studies would tend to show further that while the effect of bile in delaying coagulation is largely counteracted by calcium, yet bile has in addition an inhibitory effect on the formation of thrombin and on the action of thrombin already formed. Moreover, bile in very strong concentration in vitro entirely prevents coagulation even in the presence of an excess of calcium. It is to be doubted, however, if in obstructive jaundice such concentration of bile ever occurs as will entirely prevent coagulation of blood.

Clinically this need of calcium can be met by the administration of any calcium salt. We have mainly used calcium lactate in the dosage of 100 grams a day. We must administer calcium over a period of several days before any marked effect on the coagulation time is seen. It is evident that the necessity of employing large doses depends on the difficulty of securing the absorption of calcium from the gastrointestinal tract rather than the need of such large amounts of calcium.

In a dog, and presumably in human beings, prompt effect on the coagulation time can be obtained by the intravenous injection of calcium salts in solution. Apparently calcium can be given in this way without bad results, but its effect on the coagulation of the blood is transitory.

From a clinical point of view it would seem desirable in all cases of obstructive jaundice to make several determinations of the coagula-

tion time by the methods we have described. In these cases of obstructive jaundice relatively large doses of calcium should be given by mouth in order to meet the excessive demand for calcium which is present in this condition. The early administration of large doses of calcium seems particularly important in cases in which a deficiency in the available calcium as shown by the "calcium in vitro" test and in cases which may subsequently demand surgical interference. When an immediate effect is desired the intravenous administration of calcium is indicated and seems to have no bad effects.

COMPLEMENT FIXATION IN PERTUSSIS *

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Since Bordet and Gengou in 1906¹ announced the discovery of the etiological cause of whooping cough, basing their claim mainly on the complement fixation reactions given by the serum of whooping cough convalescents, complement fixation has been studied by many serologists both from an etiological and from a diagnostic standpoint

Bordet and Gengou used as antigen a saline emulsion of a culture of the Bordet-Gengou bacillus on solid medium. Four hours at room temperature were allowed for fixation, and readings were made the following day. In later publications² the constancy of a positive complement fixation reaction among convalescents is reaffirmed, but no figures are given. The work of Bordet and Gengou has been confirmed more or less completely by some investigators and by others their claim has been declared invalid. Meier³ found the serum of pertussis patients to react with an extract of the lung tissue of patients dying of pertussis. Arnheim⁴ using an antigen of the Bordet-Gengou bacillus, obtained positive reactions in six out of twelve cases and thought imperfect technic might account for the lack of a positive reaction in the other cases. In a later publication⁵ he stated that these twelve cases were tested again and also three others, and that by making the readings immediately instead of on the following day, as before, he obtained a positive reaction in twelve of the fifteen. The antigen consisted of an aqueous emulsion heated at 58 to 60 C for one hour, shaken on the following day for three hours and centrifuged. Fraenkel⁶ tested the serum of five pertussis convalescents against an antigen of the Bordet-Gengou bacillus and obtained a positive reaction

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1 Bordet and Gengou. Le microbe de la coqueluche, *Ann de l'Inst Pasteur*, 1906, xx, 731

2 Bordet and Gengou. Note complémentaire, *Ann de l'Inst Pasteur*, 1907, xxi, 720, Note Complémentaire sur le microbe de la coqueluche et sa variabilité au point de vue du serodiagnostics et de la toxicité, *Centralbl f Bakteriologie*, orig., 1912, lxxi, 276

3 Meier, G. Anwendung der Komplementbindungsmethode bei Keuchhusten, *Deutsch Med Wchnschr*, 1907, xxxiii, 1558

4 Arnheim, G. Ueber den gegenwertigen Stand der Keuchhusten Frage, *Berl klin Wchnschr*, 1908, xlv, 1453

5 Arnheim, G. Keuchhustenuntersuchungen, *Arch f Kinderh*, 1909, 1, 296.

6 Fraenkel, C. Untersuchungen zur Entstehung des Keuchhustens, *Munchen, med Wchnschr*, 1908, lv, 1683

in only one, though his technic was apparently the same as Bordet's Seiffert⁷ mentions a positive complement fixation reaction given by one case of whooping cough, against an antigen of the Bordet-Gengou bacillus Klimentko⁸ has reported one case, convalescent three weeks, that gave a positive reaction with a Bordet-Gengou antigen Wollstein⁹ tested the serum from nine patients, in the first to the ninth week of the disease, against antigens of the Bordet-Gengou bacillus and the influenza bacillus, and all results were negative She used as antigens salt solution suspensions of the Bordet-Gengou bacillus prepared according to the method of Bordet and Gengou, extracts of the bacilli, made by, suspending the growth of three blood-agar slants in 5 c c of salt solution and shaking twenty-four hours in the thermostat, and extracts from the lungs of a case that came to necropsy, prepared according to the method of Wassermann and Meier Menschikoff¹⁰ reported positive results with the serum of two pertussis convalescents, using antigens of the Bordet-Gengou bacillus Later Baecher and Menschikoff¹¹ found the serums of whooping cough cases examined in the first to the sixth week of the paroxysmal stage, to have no complement fixation power, but positive reactions were obtained with the serums of cases repeatedly vaccinated Four hours at room temperature were considered necessary for the fixation of complement The antigen used was a saline emulsion of Bordet-Gengou bacilli Twenty-one treated cases were tested, nine of which gave a positive reaction Finizio¹² tested the serum of eight convalescents and obtained six positive reactions with an antigen of the Bordet-Gengou bacillus Poleff¹³ tested two cases in a late stage of whooping cough, using as antigen a saline suspension of two strains of the Bordet-Gengou bacillus, and the results were negative Imai¹⁴ in testing the blood of convalescents by complement fixation confirmed the results of Bordet and Gengou

7 Seiffert, G Ueber den Bordetschen Keuchhustenbazillus, Munchen med Wchnsch, 1909, lvi, 131

8 Klimentko, W N Die Aetiology des Keuchhustens, Centralbl f Bakteriologie, orig, 1909, xlviii, 64

9 Wollstein, M The Bordet-Gengou Bacillus of Pertussis, Jour Exper Med, 1909, xi, 41

10 Menschikoff, W Ueber den Erreger des Keuchhustens, Russk Vrach, 1909, p 1044

11 Baecher and Menschikoff Ueber die Aetiologische Bedeutung des Bordetschen Keuchhustenbacillus und den Versuch einer spezifischen Therapie, Centralbl f Bakteriologie, orig, 1911, lxi, 218

12 Finizio, G Der Bordet-Gengousche Bacillus in der Aetiology des Keuchhustens, Ztschr f Kinderh, orig, 1911, iii, 121

13 Poleff, L Ueber den Bordet-Gengouschen Keuchhustenbacillus, Centralbl f Bakteriologie, orig, 1913, lxi, 23

14 Shiga, Imai and Eguchi Eine Modification von Bordet-Gengous Nahrungsboden fur die Keuchhustenbacillen nebst einigen Ergebnissen in serologischer Beziehung, Centralbl f Bakteriologie, orig, 1913 lxi, 104

Bordet and Gengou¹⁵ in 1911 called attention to the value of complement fixation in diagnosing cases of pertussis without a whoop or other typical symptom and mentioned one such case, an adult. Gengou and Brunard¹⁶ had previously reported positive complement fixation reactions with the serum of three adults who had been coughing for two months and who undoubtedly had whooping cough. Delcourt¹⁷ had likewise demonstrated the diagnostic value of complement fixation by obtaining positive reactions in seven doubtful cases of pertussis. Netter and Weil,¹⁸ working with the Bordet-Gengou bacillus, found complement fixing substances to develop too late to be of service in the diagnosis of whooping cough in normal cases. With one exception (a child that had been whooping six days) they obtained no positive reactions even by the use of active serum earlier than the second week of the whoop. During the second week active serum was found to give more positive reactions than inactive. After the fifteenth day all sixteen cases tested reacted positively, whether active or inactive serum was used. In regard to the duration of the complement fixation reaction, Weil¹⁹ claimed that a positive reaction was always given within three months of cure and might be given thirteen years after cure. He based this statement on a study of nine patients who had been cured for from two months to thirteen years. Weil suggests that other diseases, for example, measles, may have an effect on the complement fixation reaction in pertussis. Of three cases of measles that had been whooping three to five weeks, he found two to give a negative complement fixation reaction with a Bordet-Gengou antigen and the other one to give only a weakly positive reaction. Friedlander and Wagner²⁰ have reported positive complement fixation results in all stages of pertussis, including the early catarrhal, and consider the test of great diagnostic value. Their antigen is a saline emulsion of a seventy-two hour growth of the Bordet-Gengou bacillus on ascitic fluid agar. They have used active serum. A water bath at 37 C was used for fixation and incubation and readings were made within an hour after the addition of cells and amboceptor. Friedlander and Wagner

15 Bordet and Gengou. Le diagnostic de la coqueluche fruste par la methode de la fixation d'alexine, *Centralbl f Bakteriol*, orig, 1911, lvi, 573

16 Gengou and Brunard. Apropos du diagnostic de la coqueluche chez l'adulte, *Bull de l'Acad Roy de méd de Belgique*, 1910, xxiv, 329

17 Delcourt. Diagnostic de la coqueluche fruste par la Réaction de Bordet-Gengou, *Arch de méd d enfants*, 1911, xiv, 30

18 Netter and Weil. La déviation du complément par le bacille de Bordet-Gengou dans la coqueluche, *Comp rend Soc de biol*, 1913, lxxiv, 236

19 Weil, M. La deviation du complément vis-à-vis du bacille de Bordet-Gengou dans la coqueluche, *Compt rend Soc de biol*, 1913 lxxiv, 260

20 Friedlander and Wagner. Diagnosis of Whooping Cough by the Complement-Deviation Test, *Jour Am Med Assn*, 1914, lxii, 1008, *Am Jour Dis Child*, 1914, viii, 134

Strain	History	Characteristics		
		Morphological	Cultural	Serological
P D	From another laboratory, originally from Prof Bordet	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet Gengou strains
55	From sputum of a case in the sixth day of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet-Gengou strains
81	From sputum of a very severe case in the fifth day of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet Gengou strains
93	From a throat swab of a case in the eighth day of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet Gengou strains
95	From sputum of a very severe case in the first day of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet-Gengou strains
98	From sputum of a case not whooping but developing whoop later	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet-Gengou strains
100	From sputum of a case in the third day of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet-Gengou strains
114	From sputum of a case with doubtful whoop	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet-Gengou strains
121	From sputum of a case in the first day of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet Gengou strains
141	From sputum of a case in the second week of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet-Gengou strains
154	From sputum of a case in the second week of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet-Gengou strains
155	From sputum of a case in the third week of the paroxysmal stage	Typical Bordet Gengou	Typical Bordet Gengou	Fixation with all other Bordet-Gengou strains
C	Probably from pertussis, isolated about two years	Atypical Bordet Gengou	Atypical Bordet Gengou Grows without blood	Fixation with all other Bordet-Gengou strains No cross fixation
I	From sputum isolated about one year, no record of source	Atypical Bordet Gengou	Atypical Bordet Gengou Grows without blood	Some cross fixation with Bordet Gengou strains
31	From sputum of case in third week of paroxysmal stage	Atypical Bordet Gengou	Atypical Bordet Gengou Grows without blood	Some cross fixation with Bordet Gengou strains and with 10
1C	From sputum of case in third week of paroxysmal stage	Atypical Bordet Gengou	Atypical Bordet Gengou Grows without blood	Some cross fixation with 31
33	From sputum of case in second week of paroxysmal stage	Typical influenza bacillus	Hemoglobinophilic bacillus	Fixation with some other influenza strains
35	From sputum of case in fourth week of paroxysmal stage	Typical influenza bacillus	Hemoglobinophilic bacillus	Fixation with some other influenza strains
37	From sputum of case in second week of paroxysmal stage	Typical influenza bacillus	Hemoglobinophilic bacillus	Fixation with some other influenza strains
87	From sputum of case in first week of paroxysmal stage	Typical influenza bacillus	Grew several generations on asetic, then became hemoglobinophilic	Fixation with some other influenza strains
747	From spinal fluid of case of cerebrospinal meningitis	Typical influenza bacillus	Hemoglobinophilic bacillus	Fixation with some other influenza strains
BI ₂	From another laboratory	Typical influenza bacillus	Hemoglobinophilic bacillus	Fixation with some other influenza strains
Z	From spinal fluid of case of cerebrospinal meningitis	Typical influenza bacillus	Probably hemoglobinophilic bacillus	Fixation with some other influenza strains

obtained a positive complement fixation test in all eighteen cases tested in the paroxysmal stage. Of twelve cases in the catarrhal stage, from one to five weeks before the appearance of the whoop, eleven gave positive reactions. One case of doubtful pertussis gave a positive reaction. Sixteen normal individuals were negative.

The Bordet-Gengou bacillus is not the only one that has been found to give a positive complement fixation reaction with the serum of pertussis cases. Manicatide,²¹ who claims to have discovered in *Bacillus Z* the etiological factor in pertussis, has found the serum of nineteen whooping cough cases to give a positive complement fixation reaction with an antigen of *Bacillus Z*. Negative reactions were given by six normals.

The variation in the results of different workers may be explained partly by differences in technic, such as, method of preparing antigen, amount of antigen used in test, amount of serum used in test, use of active or inactive serum, time and temperature allowed for fixation, interval between the addition of sensitized cells and the reading of results, method of reading reactions, partly by a difference in the interval between taking and testing the blood specimens, and partly by the small number of cases tested. An explanation of some discrepancies is still to be found. It is difficult to reconcile Manicatide's findings with those of Bordet and his followers.

The objects of our investigation were to test the validity of the claim for the etiological relationship of the Bordet-Gengou bacillus to whooping cough and to determine the diagnostic value of complement fixation in this disease. Various strains of the Bordet-Gengou bacillus, of atypical Bordet-Gengou bacilli and of hemoglobinophilic bacilli have been classified according to their complement fixation reactions by elaborate cross titrations of immune rabbit serum and this work is soon to be described in another article.

The strains²² used for antigens in the tests with human serum are described in Table 1. The typical Bordet-Gengou bacilli may, according to their reactions with immune rabbit serum, be considered practically identical, closely related to the hemoglobinophilic bacilli but distinct from them. The atypical Bordet-Gengou bacilli are (with the exception of C) more or less closely related to each other and to the typical Bordet-Gengou bacillus. The hemoglobinophilic strains are more or less closely related to each other.

21 Manicatide. Der Komplementbindungsvorgang bei Keuchhusten, *Ztschr f Kinderh*, 1913, vii, 226.

22 Most of the strains were isolated by Dr. A. W. Williams and Miss M. A. Wilson and the morphological and cultural identification was made by them (Williams, A. W. The Etiology of Pertussis, *Arch Pediat*, 1914, xxxi, 567.)

Antigens have been prepared by Dr O Povitzky as follows. For the four atypical Bordet-Gengou strains, which grow on plain veal agar, Dr McNeil's method of preparing gonococcus antigen has been successfully employed. Twenty-four hour cultures on salt free veal agar are washed off with sterile neutral distilled water, the emulsion is heated in a water bath at 56 C for three hours, and at 80 C for one hour and filtered through a Berkefeld filter. Influenza antigens are prepared from a twenty-four to forty-eight hour growth on 1 to 500 blood veal agar, washed off with sterile neutral distilled water, shaken for two to four hours, left in a thermostat at 56 C for about eighteen hours and centrifuged or filtered through a Berkefeld filter. Antigens are prepared from the typical Bordet-Gengou strains in the same manner except that Bordet-Gengou potato-blood-agar medium is used and the growth, instead of being washed off, is scraped off with a platinum spud and deposited in the distilled water, in order to avoid extraction from the medium of substances that would render the antigen anticomplementary and nonspecific.

Inaba's²³ antigen, prepared by emulsifying three loops of a forty-eight hour culture in 5 c c of physiological salt solution, shaking one to two hours for two days and centrifuging, has been tried but has proved to be no more satisfactory than our antigens, that is, no more specific and of no more value in reacting with the serum of pertussis cases. The antigen described by Friedlander and Wagner,²⁴ a saline emulsion of a seventy-two hour growth on ascitic agar, has also been tried. The tests on whooping cough cases have been too few to be conclusive, but thus far this antigen has given no more positive reactions than ours and has seemed to be less specific. It has given strong + (doubtful) reactions with serums from normal adults, and it has cross-fixed with the serums of rabbits immunized against atypical Bordet-Gengou strains and influenza strains. Furthermore, it has the disadvantages of all live culture antigens: it must be fresh and it must be standardized immediately before use.

Antigens are standardized at the temperature to be used for tests by determining the antigen unit with a homologous immune serum and the anticomplementary dose of the antigen. For tests one-quarter the anticomplementary dose is chosen, provided that amount gives complete inhibition with the homologous serum, and the antigen is diluted so that 0.1 c c contains the desired amount. Best results, strongest and most specific, are obtained with an antigen of long range. An antigen of short range has occasionally been used in an amount greater than one-quarter the anticomplementary dose, but the results are likely to be unsatisfactory.

For a hemolytic system we have used sheep cells in a 5 per cent suspension, rabbit amboceptor and guinea-pig complement in a 10 per cent dilution. The system is carefully standardized daily by means of an amboceptor titration and for tests between two and three units of amboceptor are employed. The erythrocyte suspension is sensitized before use. The size of the test is one-tenth that of the classical Wassermann, 0.5 c c instead of 5 c c.

23 Inaba, I. Ueber den Bordet-Gengouschen Keuchhustenbacillus, *Ztschr f Kinderh*, 1912, iv, 252.

24 Friedlander and Wagner. Diagnosis of Whooping Cough by the Complement-Deviation Test, *Am Jour Dis Child*, 1914, vii, 134.

The patient's serum is tested in two amounts, 0.02 cc and 0.01 cc and the anticomplementary property of the serum is determined by 0.04 cc and 0.02 cc controls. All specimens have been tested inactive and a few comparative tests have been made with active serum.

For fixation a water bath or incubator at 37 C has been used for some tests on all specimens, and the results of these tests only are given in the accompanying tables. A few comparative tests have been made at room temperature for four hours and at ice-box temperature for four hours. For the second incubation, the water bath is invariably used and the tests are read as soon as the controls, double the amount of antigen used with the serum and double the maximum amount of serum used, are completely hemolyzed. Citron's²⁵ standard of readings is followed and only those tests are considered positive in which 0.02 cc of serum gives complete inhibition of hemolysis.

Tests have been made on specimens of serum from one hundred eleven pertussis cases or suspected pertussis cases (Table 5). Nineteen of these specimens were received when no Bordet-Gengou antigens were on hand and so were tested against atypical Bordet-Gengou strains and hemoglobinophilic strains only. With these antigens no serum, inactive, gave a positive reaction. Of eleven specimens tested active, three gave a positive reaction with strain C and one with strain BI₂.

Tables 2, 3 and 4 contain the results of tests by water bath or incubator fixation on the inactivated serum of the ninety-two specimens that were tested against Bordet-Gengou antigens. The specimens are divided into three groups, namely, those from unvaccinated cases of pertussis (Table 2), those from vaccinated cases of pertussis (Table 3), and those from prophylactic cases, i. e., cases that received vaccine before or after exposure to whooping cough and that did not develop a whoop (Table 4). Forty-eight unvaccinated cases were tested, thirty-two in the first to the seventeenth week of the paroxysmal stage and sixteen in the first to the twenty-first week of convalescence. Twelve of the whooping cases gave a positive reaction with at least one Bordet-Gengou antigen, a percentage of 37.5, and two of the convalescents gave a positive reaction, a percentage of 12.5. The earliest case tested had been whooping two days. The earliest case that gave a positive reaction had been whooping five days. The total number of vaccinated cases tested was thirty-two, six in the fourth to the seventh week of the paroxysmal stage and twenty-six in the first to the twelfth week of convalescence. Three of the whooping cases gave a positive reaction with at least one Bordet-Gengou antigen, a percentage of 50, and fifteen of the convalescent cases, a percentage of 57.7. The highest percentage of positives among unvaccinated cases has been obtained in the paroxysmal stage, among vaccinated cases the highest percentage occurred after the cessation of the whoop. The number of cases is insufficient, however, to establish this as a rule.

²⁵ Citron. Immunity. Translated by Garbart, 1914, p. 184.

TABLE 3.—COMPLEMENT FIXATION REACTIONS OF INACTIVE SERUM FROM TWENTY-NINE VACCINATED CASES OF PERTUSSIS

[illegible]

The fact that the convalescent vaccinated cases were tested within the first three months of convalescence and most of the convalescent unvaccinated later, should be taken into consideration in comparing the two series (Table 6)

Two unvaccinated cases (7 and 14) were tested at two different times. The serum of Case 7 was on both occasions positive with the Bordet-Gengou antigen P D. Case 14 gave a \pm reaction the first time, a $+++$ reaction the second. This probably does not indicate a development of complement fixing substances between the first and the second bleedings, in the fifth and the seventh week, respectively, of the paroxysmal stage, but is due to the fact that the first specimen was not tested promptly and had lost antibody content when the test was made. This is the only specimen that, inactive, gave a positive reaction with antigen C, forty-seven were tested. The second specimen of Case 14 (14 b) gave a positive reaction with Antigen 1, only one other specimen (110) out of twenty-nine tested against Antigen 1 gave a positive reaction with this strain. Cases 7 b and 14 b were the only specimens out of nine to give a positive reaction with the hemoglobinophilic strain 35. Case 14 b also gave a positive reaction with BI₂, which appears to be less closely related than any other hemoglobinophilic strain studied to the Bordet-Gengou bacillus, tests on thirty-five other specimens from pertussis cases were negative or doubtful. Whether these reactions of 7 and 14 were nonspecific, due to undeveloped technique, or the poor antigens with which the work was begun, or whether they were due to a mixed infection in the cases, is not known. All tests with antigens 31, 10, 33, 37, 747 and Z have been negative or doubtful. The positive reactions given by antigen 87 are of special interest, as this strain was obtained from the sputum of a pertussis case. Of twenty-seven specimens tested against this strain, five (18.5 per cent) have given positive reactions, and one of these (43) also gave a positive reaction with the Bordet-Gengou strain 55. The total number of specimens tested against antigens of hemoglobinophilic strains is sixty, the total number giving a positive reaction is six.

There is a marked lack of uniformity among the reactions given by different Bordet-Gengou strains with the same serum. This may be partly due to an inherent difference in the strains that has not been apparent in the cross-titrations, this point is to be investigated later. One reason is a difference in the range of the antigens, the longer the range of an antigen, the more likely it is to give the maximum number of specific fixations. Another reason for the lack of uniformity, unfortunately only recently observed, is the instability of an antigen after the addition of the salt. The aqueous extract antigens that have been used are stable for many months, but after being made isotonic they

TABLE 4—COMPLEMENT FIXATION REACTIONS OF INACTIVE SLURM FROM TWELVE VACCINATED CASES WHICH DID NOT DEVELOP INTO TYPICAL PERTUSSIS

Serial Number	Symptoms	Vaccine Administered	Amount Vaccine in Millions	Interval Between First Vaccination and Complement Fixation Test	Antigens Used														
					P	D	55	81	93	95	98	100	O	31	10	87	717	DI ₂	
70	Slight cough	1	1,040	50 days	±		+			±	+							+	+
75	Cough	1	850	2 mos	—		—											—	
65	Occasional cough	1	1,750	39 days	—														
66	None	1	650	57 days	—		—												
69	Cough for two weeks	1 2	1,350 1,000	43 days	+++		++												
70	Bronchitis	1 2	3,350 2,500	36 days	±		—												
71	None	1	850	57 days	+		—												
73	Cough two weeks	1 2	1,350 2,500	36 days	±		—												
74	Slight cough	1	650	57 days	—		—												
75	Slight cough	1	650	43 days	—		—												
89	Cough	3							±										
92	Cough	5																	

lose fixing power and cannot be depended on for more than two or three days. This fact undoubtedly accounts for some of the negative and doubtful reactions among convalescent cases and those late in the paroxysmal stage. Some serologists would probably consider positive many of the $+$ reactions, those in which there is only slight hemolysis in the tube containing 0.02 c.c. of serum. Many of these reactions undoubtedly are specific, but inasmuch as a reaction of the same strength may be given by an antigen of a closely allied organism that is not the infecting agent, it seems wise to hold to the rule of calling only $++$, $+++$ and $++++$ reactions positive. Only cases of pertussis have given $++$, $+++$ and $++++$ reactions. The presence of natural antisheep amboceptor in the patients' serum has not been taken into consideration and may account for some doubtful and negative reactions.

TABLE 5—SUMMARY OF COMPLEMENT FIXATION REACTIONS AMONG 111 CASES OF PERTUSSIS INCLUDING TWELVE DOUBTFUL CASES DESIGNATED AS PROPHYLACTIC

		Number Positive	Percentage Positive
Number cases tested	111		
Cases not tested against Bordet Gengou antigens	19		
Cases tested against Bordet Gengou antigens	92	33	35.9
1 Vaccinated cases of pertussis	32	18	56.2
Vaccinated cases whooping	6	3	50.0
Vaccinated cases convalescent	26	15	57.7
2 Not vaccinated cases of pertussis	48	14	29.2
Not vaccinated cases whooping	32	12	37.5
Not vaccinated cases convalescent	16	2	12.5
3 Doubtful cases of pertussis—vaccinated	12	1	8.3

Complicating infections, such as measles and scarlet fever, may, as suggested by Weil,¹⁹ cause a weakening of the complement fixation reaction for whooping cough. We have tested only four cases suffering from both measles and pertussis. The four all gave negative reactions with antigen P D, but as they had been whooping only two, four, eleven and fifteen days, respectively, this result was not to be wondered at. The three scarlet fever cases had been whooping one, five and six weeks, respectively, and the second gave a positive reaction with antigen 81. Owing to the low percentage of positive reactions among cases of pertussis without complications, these tests prove nothing as to the effect of other infections on the antibodies of the Bordet-Gengou bacillus.

Among sixty-seven specimens of serum from normals or from patients suffering from some disease other than pertussis (chiefly syphilis or gonococcus infection), no positive reaction has been given by inactive serum with a Bordet-Gengou or an atypical Bordet-Gengou antigen. Tests with influenza antigens have also been negative, with the exception of two positive reactions with BI₂ and one with 87. As an influenza infection in these three individuals prior to the taking of the blood specimens could not be excluded, there was no proof of the nonspecificity of the reactions.

TABLE 6—COMPLEMENT FIXATION REACTIONS AMONG SIXTEEN UNVACCINATED AND TWENTY-SIX VACCINATED CONVALESCENT CASES OF PERTUSSIS^a

Weeks of Convalescence	Not Vaccinated (16 Cases)	Vaccinated (26 Cases)
1	+ -	+ + - -
2	-	+ +
3		+ -
4		+ -
5		+ + -
6		- -
7		+ + +
8	-	+ + - -
11		+
12	-	+ - -
13	-	
15	- -	
16	- - -	
17	-	
18	-	
20	+ - -	

* Each + symbol denotes one case having positive reaction Each — symbol denotes one case not having positive reaction

[illegible]

That the administration of vaccine has an effect on the complement fixation reaction of pertussis cases seems indisputable, but it is doubtful if complement fixing substances would develop in the serum as the result of vaccine alone. Among the twelve vaccinated children that did not develop typical whooping cough (Table 4), the serum of one only, who had coughed for two weeks, gave a positive complement fixation reaction with two Bordet-Gengou antigens (a percentage of 83) and this was probably a case of whooping cough running a short atypical course. Two normal adults, inoculated with large doses of

TABLE 7—RESULTS OF SUCCESSIVE INCREASING DOSES OF PERTUSSIS VACCINE ON COMPLEMENT FIXATION IN THE CASE OF TWO NORMAL ADULTS

Results																	
	Date of Infection	Amount of Vaccine injected in Millions	Reaction	Date of Bleeding	Date of Test	Antigen P D		Antigen 98		Antigen O		Antigen 10		Antigen B1a		Antigen Z	
						Active Serum	Inactive Serum	Active Serum	Inactive Serum	Active Serum	Inactive Serum	Active Serum	Inactive Serum	Active Serum	Inactive Serum	Active Serum	Inactive Serum
O (Had pertussis 21 yrs ago)	4/ 1/14	125		4/ 1/14	4/ 7/14	++++	-					+++	-	+++	-		
	4/ 4/14	250	Local	4/ 7/14	4/ 7/14	±	-					-	-	-	-		
	4/ 7/14	500	Strong local														
	4/11/14	1,000	Local and slight general														
	4/21/14	2,000	Strong general, headache, dizziness, etc	4/20/14	5/ 4/14	Strong +	+			±	±	±	±		Strong +		±
L (Never had Pertussis)	4/ 1/14	125		4/ 1/14	4/ 7/14	Strong +	-	-	-			-	-	±	-		
	4/ 4/14	250		4/ 7/14	4/ 7/14	-	-	-	-			-	-	-	-		
	4/ 7/14	500	Local				+	-	-								
	4/11/14	1,000	Strong local	4/11/14	4/20/14												
	4/14/14	2,000	Slight general, temperature 99.1														
	4/21/14	4,000	Temperature 100.2, muscular weakness	4/20/14	5/ 4/14	Strong +	+			±	±	±	±		+++	+	±

vaccine (Table 7), at no time gave a positive complement fixation reaction when inactive serum was used. Before the first inoculation a positive reaction was given by the active serum of O, who had had pertussis twenty-one years before, with antigens P D, 10 and BI₂. The active serum of L, who never had had pertussis, gave a positive reaction after the sixth injection with antigen Z but several months before this experiment was performed his active serum gave a positive reaction with antigen C.

TABLE 8—RESULTS OF SEVENTY-SEVEN COMPARATIVE COMPLEMENT FIXATION TESTS WITH THE ACTIVE AND INACTIVE SERUM OF THIRTY SPECIMENS FROM CASES OF PERTUSSIS

Antigens	Number of Specimens Tested	Number of Specimens Giving Positive Reaction	
		Serum Inactive	Serum Active
P D	10	0	2
O	22	1	4
I	9	0	0
31	12	0	0
10	1	0	0
S7	1	0	0
BI ₂	16	0	3
Gonococcus	6	0	5

These tests on the serum of normal adults demonstrate the danger of making false diagnoses by using active serum. In determining the etiology of pertussis, active serum is of little value. We have tested thirty specimens from pertussis cases, active as well as inactive, some with several antigens, so that seventy-seven comparative tests have been made (Table 8). Of ten tests with P D two more positives were obtained with active serum. Of twenty-two tests with C three more positives were obtained with active serum. Of sixteen tests with BI₂, positives were obtained with active serum only, three in number. Five specimens from whooping cough cases with no history of gonococcus infection gave a positive reaction with a specific gonococcus antigen when tested active; the inactivated serum reacted negatively or doubtfully. Most of the specimens of active serum used as negative controls in the pertussis tests gave negative or doubtful reactions with antigens of the Bordet-Gengou bacillus, but even an occasional false positive is sufficient to destroy the diagnostic value of the test. A negative reaction given by active serum is stronger evidence of the lack of a specific infection than is a negative reaction given by inactive serum;

but a positive reaction given by active serum is, in our experience, no proof of the presence of a specific infection

The tests made at room temperature for four hours and at ice-box temperature for four hours have been too few to warrant the drawing of conclusions concerning the value of either method as compared with water bath or incubator fixation, but they are sufficient to show that not all convalescent cases of whooping cough give a positive reaction even when four hours are allowed for fixation. Eighteen specimens (eight vaccinated convalescents, nine unvaccinated convalescents and one vaccinated doubtful case) were tested against Bordet-Gengou antigens by both water bath and room temperature methods and four more positives (22.2 per cent) were obtained by the latter method. Two of these were among vaccinated convalescents, one was an untreated convalescent and the fourth was a prophylactic case. Five vaccinated convalescents gave positive reactions by both methods, one vaccinated convalescent was negative by both, eight untreated convalescents were negative or doubtful in both. Other tests were made that could not be read at all, owing to the anticomplementary action of the antigens. When the temperature of the room is so variable that a standardization of the antigen is no guide to the amount of antigen to be used in the test, this method is not of practical value. We have not tested enough negative controls by the room temperature method to be certain of the specificity of the reaction. Experience in the diagnosis of other infectious diseases by means of complement fixation led us to suppose that constant and reliable results would be obtained by ice-box fixation and a higher percentage of positives than by water bath or incubator fixation. The number of tests made is insufficient to establish this. Thirteen specimens have been tested against Bordet-Gengou antigens, allowing four hours for fixation. Only two more positives (15.4 per cent) were obtained by this method than by water bath fixation. One was in the case of a vaccinated convalescent, the other an untreated convalescent. One specimen gave a positive reaction by both methods. Of the nine specimens that gave a negative or doubtful reaction by both methods one was from a vaccinated whooping case, one from a vaccinated convalescent and the other seven from untreated cases still whooping. A longer period than four hours would probably give equally specific results and more positive reactions.

As our technic improved the percentage of positive reactions given by the serum of pertussis cases has increased, but even among pertussis convalescents the number of positive reactions is still far below 100 per cent. Even though the power of fixing complement with antigens of the Bordet-Gengou bacillus is not constantly present in the

serum of these cases, the frequency of a positive reaction is so great as to be presumptive evidence of the etiological relationship of the Bordet-Gengou bacillus to whooping cough

SUMMARY

1 The most reliable antigen for complement fixation tests in whooping cough is obtained by autolyzing an aqueous emulsion of a twenty-four to forty-eight hour growth of the Bordet-Gengou bacillus for eighteen to twenty-four hours at 56 C and shaking for several hours. The closeness of relationship of the Bordet-Gengou strains is still under investigation. To obtain the maximum number of positive reactions it may be necessary to use a polyvalent antigen.

2 Active serum may give non-specific positive reactions. A negative reaction given by active serum is stronger evidence of the lack of an infection than is a negative reaction given by inactive serum.

3 For fixation one-half hour in the water bath or one hour in the incubator is absolutely reliable. Ice-box fixation probably gives reliable results, the optimum period is still to be determined. Fixation at room temperature for four hours is unsatisfactory, at least in rooms with variable temperature.

4 About 40 per cent of whooping cough cases have given a positive reaction with antigens of the Bordet-Gengou bacillus, when inactive serum was used. The highest percentage of positives is given by convalescent vaccinated cases. Ten per cent of whooping cough cases have given a positive reaction with antigens of hemoglobinophilic strains.

5 A ++, +++, or ++++ reaction by inactive serum with an antigen of the Bordet-Gengou bacillus is diagnostic of whooping cough, a + or = reaction is suspicious, a negative reaction has little significance.

CONCLUSIONS

Complement fixation tests on serum from one hundred eleven cases of pertussis or suspected pertussis support the theory that the Bordet-Gengou bacillus is the etiological factor in the disease. The complement fixation test may be of value in the diagnosis of doubtful cases of pertussis.

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THREE CASES SHOWING CHANGES IN THE LOCATION OF THE CARDIAC PACEMAKER ASSOCIATED WITH RESPIRATION †

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THE EFFECT OF VAGUS STIMULATION ON THE PACEMAKER

Under experimental conditions, the heart rate in certain animals varies with each phase of respiration and the relationship is such that the longest diastolic pauses occur during expiration, and the shortest pauses during inspiration. Clinically, exactly similar changes in heart rate are common in children and adolescents, and in adults who are nervous or who are recovering from acute illnesses. They are increased by deep breathing and under such conditions are almost universal. The fact that these changes in heart rate disappear after atropin, or after section of the vagi in animals, demonstrates that they are vagal in origin.

Recent experimental studies by Meek and Eyster¹ and by Lewis, Meakins and White² have shown that stimulation of the right vagus may cause the pacemaker to migrate from the upper to the lower portion of the sino-auricular node. Stronger stimulation of the right vagus may, in a small percentage of animals, produce an auriculoventricular rhythm^{3,4}. After an auriculoventricular rhythm has been produced by this or other means, stimulation of the vagus may cause the pacemaker to shift from the upper portion of the auriculoventricular node near the coronary sinus to some lower portion³. Meek and Eyster¹ have explained these phenomena by assuming that the number of fibers supplied by the vagus to the system of specialized tissue found in the heart diminishes as we move from the sinus node downward.

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1 Meek, W J, and Eyster, J A E. Experiments on the Origin and Propagation of the Impulse in the Heart. IV. The Effect of Vagal Stimulation and of Cooling Upon the Location of the Pacemaker Within the Sino-Auricular Node, *Am Jour Physiol*; 1914, xxxiv, 368

2 Lewis, T, Meakins, J, and White, P. The Excitatory Process in the Dog's Heart. Part I. The Auricles, *Phil Trans Royal Soc, London, Series B*, 1914, ccv, 375

3 Meek, W J, and Eyster, J A E. Experiments on the Origin and Propagation of the Impulse in the Heart. III. The Effect of Vagal Stimulation on the Location of the Pacemaker, the Location of the Pacemaker in Auriculoventricular rhythm, and the Effect of Vagal Stimulation on this Rhythm, *Heart*, 1914, v, 227

4 Lewis, T. The Effect of Vagal Stimulation Upon Atrioventricular Rhythm, *Heart*, 1914, v, 247

ECTOPIC RHYTHMS

Rhythms which originate at some point in the heart other than the sinus node are called ectopic rhythms. They have been divided by Lewis⁵ into two classes.

Ectopic rhythms of the first class are characterized by a sudden onset and a rapid rate. The pacemaker shifts abruptly to a new location, which may or may not lie in the specialized tissue. Lewis, who believes that the ectopic impulses in such cases are elaborated by pathologic processes, has called these rhythms heterogenetic.

Ectopic rhythms of the second class are characterized by a comparatively slow rate. The change in heart rate at the onset of the new rhythm is gradual. The change in the location of the pacemaker may be gradual or abrupt. The point of origin probably always lies within the specialized tissues. These rhythms are believed to arise in the following way. The rates of the inherent rhythms of the various parts of the system of specialized tissue diminish as we go from the sinus node downward. That portion of the specialized tissue which possesses the highest degree of automaticity at any particular time acts as pacemaker for the heart. When the rate of the sinus rhythm is reduced below the inherent rhythm of some lower center, the latter becomes pacemaker. The same thing occurs when impulses sent out by the sinus node fail to reach the lower centers because of conduction changes, as, for instance, in complete heart block, in which case the ventricular part of the a-v conduction system acts as pacemaker for the ventricles. Lewis has called ectopic rhythms of this type homogenetic. He believes that the impulses which give rise to them are elaborated by physiologic processes. While it is often possible to say with certainty that a given ectopic rhythm is heterogenetic, as for instance in auricular flutter, or homogenetic, as in idioventricular rhythm, this distinction is not always possible if the rate at which the ectopic impulses are formed closely approaches that of the normal sinus rhythm.

At the onset of a homogenetic ectopic rhythm, two centers may for a short time send out impulses at very nearly the same rate. These stimuli arising from different parts of the auricle at about the same time may meet in the auricular walls causing interference phenomena. Furthermore, at the onset of an a-v rhythm the auricles may respond to the sinus node while the ventricles respond to the a-v node. As the rates of the two centers become divergent, however, one center gains the upper hand and becomes the pacemaker of the whole heart.

⁵ Lewis, T. Exceptional Types of Slow Heart Action, *Quart Jour Med*, 1912-13, vi, 221

During the course of an ectopic rhythm of the homogenetic type, gradual changes in the location of the pacemaker within the specialized tissues analogous to those observed experimentally sometimes occur in man. Two cases recently reported by Weil⁶ showed a gradual migration of the pacemaker within the a-v node. Possibly this was produced in one of the cases by vagal pressure which was made shortly before the curve was taken. In a third case reported by the same author, the analysis of the curves was difficult, but in addition to the above changes there seemed to be an alternation of sinus and a-v rhythm and possibly also a migration of the pacemaker within the sinoauricular node.

CASE REPORTS

The following cases are unusual in that changes in the location of the pacemaker may be definitely correlated with respiration.

CASE 1—History—Mrs E. D., an American housewife, aged 34, came to the University Hospital, Jan. 12, 1915, because of an ulcerative lesion of the nose and was admitted to the dermatological service. The family history was negative. The patient had had the ordinary diseases of childhood, but had been otherwise well, except for an attack of "rheumatism" at the age of 28. Her symptoms at that time were severe pains in the legs below the knees, with swelling of the shins and violent headaches. These symptoms were associated with a general skin eruption. The lesion on the nose for which she came to the hospital appeared as a small papule in November, 1914, and gradually grew larger and ulcerated. The patient had been short of breath on exertion for about seven or eight months, but had had no other cardiac symptoms. The examination showed an undernourished woman with an ulcerative lesion affecting both alae of the nose, and a similar lesion on the left foot.

Examination—The heart apex was located in the fifth intercostal space, 15 cm. outside the midclavicular line. A marked presystolic thrill was felt over this region. Percussion showed that the right border of the heart extended 1 cm. beyond the sternal edge. There was a marked presystolic shock over the entire precordium. On auscultation a loud presystolic murmur was heard at the apex and the first sound was loud and snapping. The pulmonic second sound was accentuated. Extrasystoles occasionally interrupted the otherwise regular rhythm. The clinical diagnosis was tertiary lues and mitral stenosis. The patient was treated with neosalvarsan and during a stay of three weeks in the hospital the nose and foot lesions showed marked improvement. Electrocardiograms were taken on many different occasions.

CASE 2—History—Mr C. L., an American bookkeeper of 23, was examined as an out-patient, March 8, 1915, at the request of the Department of Genito-Urinary Surgery, in which department he was being treated for gonorrheal urethritis and rheumatism. He complained of attacks of tachycardia. The family history was negative except that one aunt died of tuberculosis of the lungs. The patient was said to have had a damaged heart valve at birth. He had had measles, scarlet fever, and a questionable typhoid during childhood. He had also had several attacks of quinsy, the first at the age of 12 and the last in the autumn of 1914. Between the ages of 10 and 12 he began to have attacks of tachycardia during which his heart rate reached 170 or more. These

⁶ Weil, A. Beiträge zur klinischen Elektrokardiographie, Deutsch. Arch. f. klin. Med., 1914, cxvi, 486.

attacks had persisted up to the time of examination. They always began and ended suddenly, exercise seemed to bring them on at first, but had not appeared to do so for the last five years. The attacks usually lasted for five or six hours and during them he felt faint and weak. In 1910 he had an attack nearly every week but since that time they had become less frequent and he had gone as long as three months without an attack. The last three attacks that the patient had had were more severe than any previous ones, the last one lasted three days and confined him to bed. The patient had stopped attacks at various times by quickly changing his position or by holding his breath. In December, 1914, he contracted gonorrhea and one week later, Jan 3, 1915, he developed a gonorrheal arthritis of the right wrist.

Examination—The heart apex was located in the fifth intercostal space, 1 cm outside the midclavicular line. The systolic impulse at this point was well sustained and was accompanied by a short thrill. The right border of the heart was not beyond the sternal margin on percussion. On auscultation, at the apex, there was a slight presystolic roughening and the first sound was loud and snappy. The second sound was accentuated. Over the fourth left costal cartilage a third sound was distinctly heard when the heart rate was slow. This sound occurred in middiastole and sounded like an echo of the second sound. It was transmitted to within 2 cm of the apex and upward to the third rib. There was a marked respiratory irregularity during forced respiration. The clinical diagnosis was mitral stenosis. Electrocardiograms were taken frequently over a period of six weeks.

CASE 3—History—Mr L D, a student of 22, was examined in the outpatient department on account of palpitation and tachycardia. His family history was negative. He had had measles during childhood, but had never had any of the other common contagious diseases. He had had an attack of tonsillitis one month previous to the examination. He denied venereal disease. He had had periods of rapid heart action for as long as he could remember. These attacks usually lasted about one week. They never began or ended suddenly. The most rapid heart rate that he had ever had was during the last attack, which began about one week before the examination. At this time his heart rate reached 140. He complained that his heart skipped beats occasionally.

Examination—The heart apex was located in the fifth intercostal space, just inside the midclavicular line. There was no enlargement on percussion and no murmurs were heard on auscultation. The first sound was loud and a third sound could be heard in middiastole when the heart rate was slow during the expiratory phase of deep respiration. Electrocardiograms were taken on several occasions.

RESPIRATORY CHANGES IN THE LOCATION OF THE PACEMAKER IN OR NEAR THE SINUS NODE

The first electrocardiograms taken soon after Patient 1 entered the hospital showed no abnormalities aside from occasional auricular extrasystoles, and a very tall broad P complex such as is commonly seen in mitral stenosis. It was noted, however, that a marked slowing of the pulse occurred on deep breathing, and a large number of records were taken during forced respiration. Figures 1, 2, 3 and 4 are examples of the curves obtained at this time.

Shortly after the beginning of expiration the heart rate slowed to less than one-half its usual rate and then gradually returned to normal. During this slowing the P complex became gradually smaller and

bifurcated in the second and third leads. The flattening of P was sometimes so marked in the third lead that it almost disappeared (Fig 4). This was never observed in the second lead. In the first lead P showed no appreciable change in height, although it became somewhat broader (Fig 1).

We have observed similar though less marked changes in the P complex in a number of patients with respiratory irregularities and changes equally as marked have been observed both experimentally and clinically by a number of authors.

A decrease in the size of the P complex has been noted in dogs by Einthoven⁷ during vagus stimulation (Lead II), by Eyster and Meek⁸ after poisonous doses of morphin (Lead II), and by Blumen-

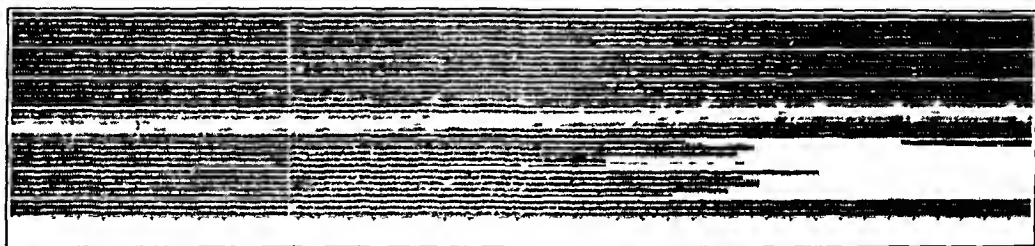


Fig 1—In this, as in the following figures, the time marker indicates fifths of a second, and an ordinate of 15 mm is equal to 1 millivolt. Lead I. A marked slowing of the heart rate with no change in the height of P.

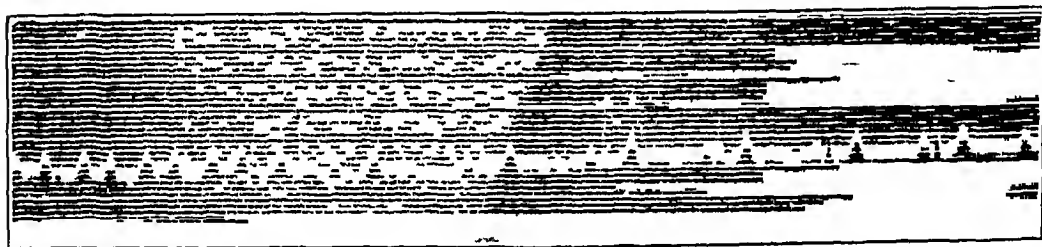


Fig 2—Lead II. The heart rate slows to less than one-half its usual rate. Coincident with this slowing, P becomes smaller and bifurcated.

feldt and Putzig⁹ during expiratory slowing (Lead II). The last two observers found an increase in the height of the P complex in Lead I. Clinically, a decrease in the height of P has been noted during vagal pressure by Ritchie¹⁰ (Lead II) and by von Hoesslin¹¹ (Leads I and

7 Einthoven, W. Weiteres über das Elektrokardiogramm, *Arch f d ges Physiol*, 1908, cxxii, 517.

8 Eyster, J. A. E., and Meek, W. J. Cardiac Irregularities in Morphin Poisoning in the Dog, *Heart*, 1912-13, iv, 59.

9 Blumenfeldt, E., and Putzig, H. Experimentelle elektrokardiographischen Studien über die Wirkung der Respiration auf die Herztätigkeit, *Arch f d ges Physiol*, 1914, clv, 443.

10 Ritchie, W. T. The Action of the Vagus on the Human Heart, *Quart Jour Med*, 1912-13, vi, 47.

11 von Hoesslin, H. Beobachtungen über den Einfluss des Vagus auf das menschliche Herz, *Deutsch Arch f klin Med*, 1914, cxiii, 537.

II), and during forced respiration by Einthoven, Fahr and de Waart¹² (Leads I, II and III) In one of the cases reported by Einthoven, Fahr and de Waart, P became negative in Lead III and the same thing occurred in Lead I in one of von Hoesslin's and in one of Ritchie's cases

A decrease in the height of P during vagus stimulation may be explained in the following ways

Changes in the contractility of the auricles Einthoven, Ritchie, and Eyster and Meek have regarded the flattening out of P as due to a diminution in the contractility of the auricles Against this explanation in the present case is the fact that no change in the height of P occurred in the first lead although a well marked one occurred in the other leads taken immediately afterward It is difficult to see, if the change in P is dependent on changes in auricular contractility, why it should be present in one lead and not in another

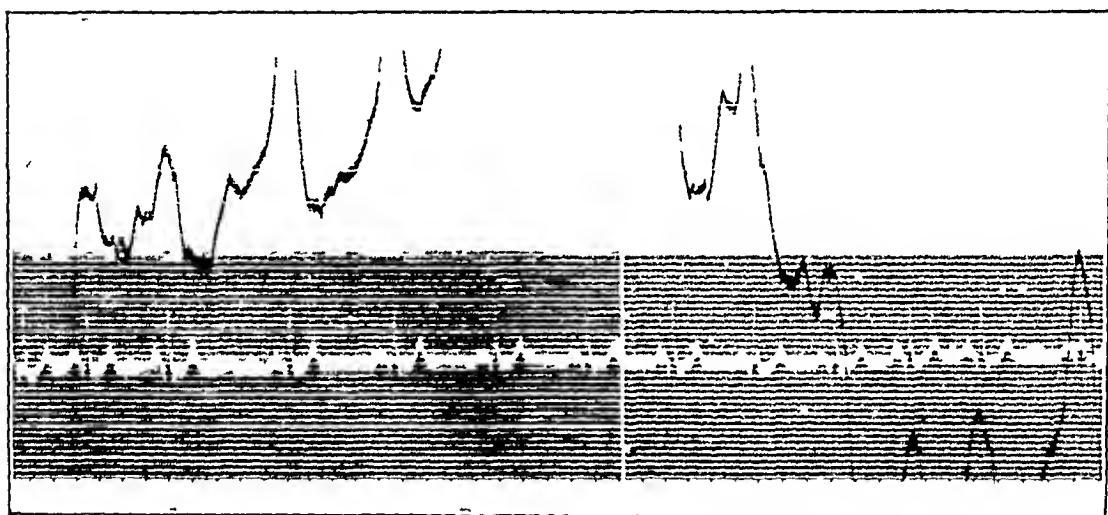


Fig 3—Lead III Shortly after the beginning of expiration (upward movement of the venous pulse record) a marked slowing of the rate with flattening of P occurs

Interference of two rhythms Flattening out of P may be due to the simultaneous origin of two contraction waves in opposite portions of the auricle, so that their electrical effects partially or completely neutralize each other Although this phenomenon occurred in the present case and will be described later, it is an improbable explanation where, as in the curves under discussion, the heart rate is constantly changing, for the rates of two centers would not be apt to change with equal speed Furthermore, the deformed P complexes due to

12 Einthoven, W, Fahr, G, and de Waart, A Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch f d ges Physiol, 1913, cl, 275

interference are followed by a shortened P-R interval and the P-R intervals of the complexes in question are normal

Changes in the position of the heart Einthoven, Fahr and de Waart have recently shown that although marked changes in the electrocardiogram may be produced by changes in the position of the heart, the changes in P which occur during forced respiration can not be due to this alone It will be readily seen in Figure 4 that if a point in inspiration be compared with a point in expiration at which the distention of the lungs and consequently the position of the heart is the same, the heights of the P complexes differ widely If the changes in P were due to changes in the position of the heart, the P complexes at these two points would be of equal height

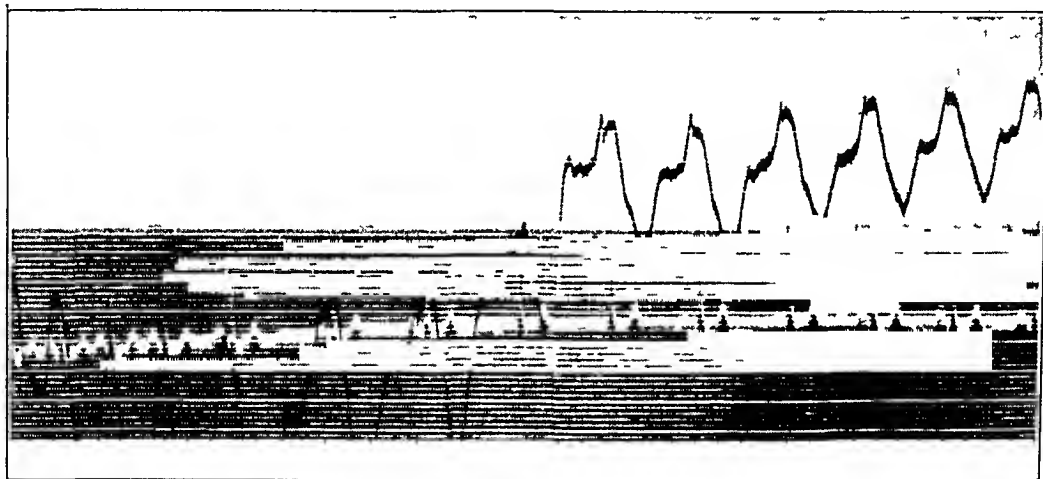


Fig 4—Lead III The reduction in the size of P is so marked that it practically disappears

Changes in the location of the pacemaker Ritchie,¹⁰ von Hoesslin,¹¹ and Einthoven, Fahr and de Waart¹² ascribed the inversion of P which they observed after vagal stimulation, to some change in the location of the pacemaker or to some change in the path of the contraction wave over the auricles Lewis¹³ has shown that a change in the shape of P indicates a change in the location of the pacemaker He found for Lead II that if the impulse originates in the upper portion of the auricle, P is upright When the impulse originates in the median portion of the auricle, P approaches the isoelectric state and when it originates in the lower portion of the auricle P is inverted In the first lead the size and direction of P may not be markedly affected even when the impulse originates in the 'a-v node'¹⁴ We

13 Lewis, T Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature *The Pacemaker of the Heart*, 1910-11, 11, 23

14 Hering, H Rhythmische Vorhofstachysystolie und Pulsus irregularis perpetuus, *Munchen med Wchnschr*, 1914, 121, 2057

believe that in the present case the gradual flattening of the P complex in the second and third leads indicates that the pacemaker has moved downward. Since this occurred as the result of deep breathing, i.e., vagal stimulation, this explanation is also in accord with the experimental evidence that stimulation of the vagus displaces the pacemaker downward in the sinus node. The amount of change which P may undergo as a result of the migration of the pacemaker to the lower end of the sinus node has not yet been determined experimentally, so that it is impossible to tell whether this explanation would completely suffice in the present case where such marked changes in the size of P occurred.

RHYTHMIC AURICULOVENTRICULAR RHYTHM PRODUCED BY DEEP RESPIRATION

On January 25 it was noted that Patient 1 no longer showed a marked slowing of the pulse on deep respiration. Curves taken on this date disclosed an entirely different mechanism from that described above. Figure 5 is a typical example of these curves. Shortly after

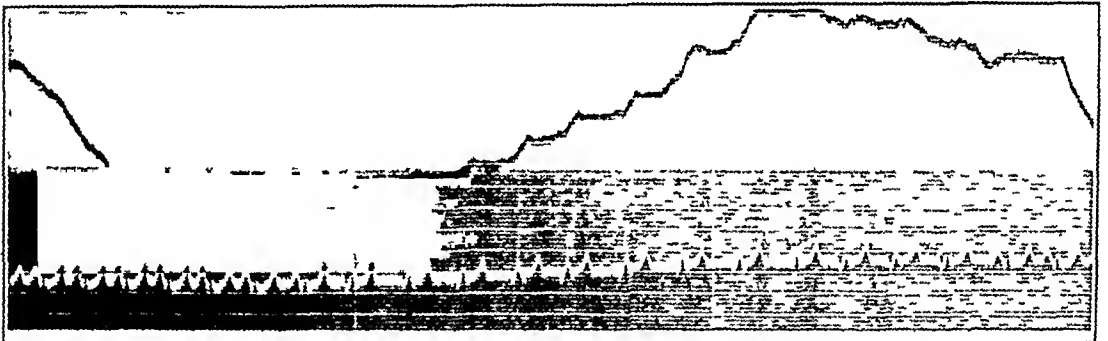


Fig 5—Lead II. Shortly after the beginning of expiration an atrioventricular rhythm appears. The P waves of this rhythm are inverted and the P-R intervals are shortened from about 0.15 seconds to about 0.09 second. The onset of the a-v rhythm is abrupt. The heart rate slows slightly at the beginning of this rhythm, but is faster than the heart rate during expiration in the previous figures. The inverted P complexes vary somewhat in form. The R complexes are unusually tall.

the beginning of expiration a slight slowing of the rate occurred. Coincident with this change in rate an abnormal rhythm appeared. This new rhythm was characterized by an inversion of P and marked shortening of the P-R interval. With the exception of a distinct increase in the height of R, the ventricular complexes were unchanged. These characteristics indicate that the site of origin of the new rhythm was in the upper part of the a-v node. The ectopic rhythm persisted for a short time and then the normal rhythm returned. This mechanism was repeated after each deep breath.

A very similar dislocation of the pacemaker could be produced in Case 2 also by forced respiration. In Figure 8, it will be seen that,

as in Figure 5, expiratory slowing is accompanied by the appearance of an abnormal rhythm. Here also the abnormal rhythm is characterized by inversion of P and shortening of the P-R interval indicating that the pacemaker was located in the a-v node. In this case the abnormal rhythm could also be produced by pressure on the right vagus in the neck. After the patient had been under observation for

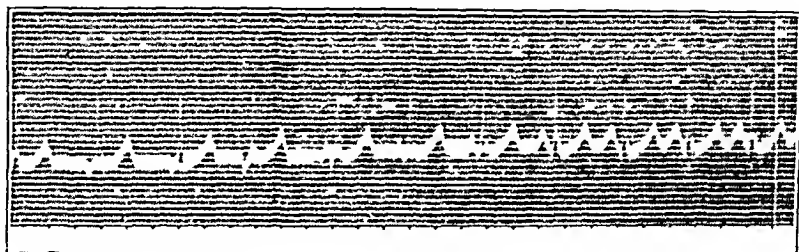


Fig 6—Lead II. Several transitional complexes occur at the end of an attack of a-v rhythm. The first two are diphasic, the third upright but small, and the fourth differs from the normal P complexes only in being more pointed. The P-R intervals of the first three transitional beats are shortened, that of the fourth is normal.

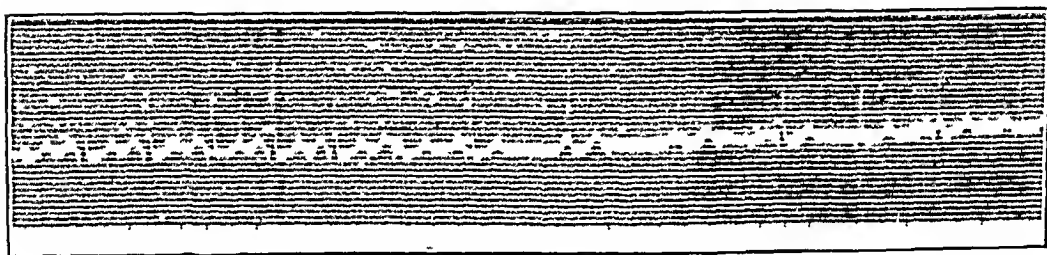


Fig 7—Lead III. The P and R complexes 9 and 10 are partially coincident. The P-R intervals are about 0.07 and 0.03 second, respectively. The P complexes are upright. The auricles responded to the sinus, the ventricles to the a-v node.

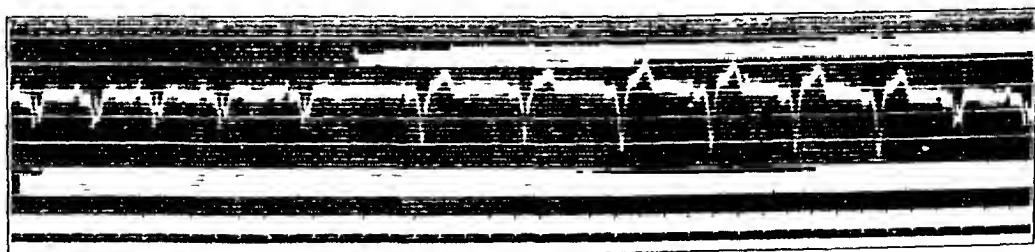


Fig 8 Case 2 Lead III. Expiratory slowing is accompanied by the appearance of an abnormal rhythm. The first two Ps of this rhythm are diphasic, the rest are inverted. The P-R intervals are shortened from about 0.17 sec to 0.1 sec. The ventricular complexes of the a-v rhythm are abnormal.

two or three days it began to appear spontaneously and at the end of a week was the rhythm usually present. During this period it could be abolished in favor of the normal rhythm by giving atropin subcutaneously in doses sufficient to paralyze the vagi. In Case 2, the ventricular complexes during the abnormal rhythm, in contrast to

those of Case 1, are strikingly abnormal. As this modification of the ventricular complexes has no bearing on the subject treated in the present article, however, it will not be discussed here.

Transitions from a-v to normal rhythm and vice versa are of considerable interest. These are sometimes abrupt (Fig 5). At other times they are more gradual, and between complexes of definite sinus origin and others of definite a-v origin two or more transitional complexes may occur (Figs 6-8). The P deflections of these complexes are of two types, they are either upright and smaller than the P deflections of sinus origin or they are diphasic.

Two explanations may be offered for such transitional beats. They may be due to the interference of two contraction waves, the result of simultaneous impulse formation at the sinus and a-v nodes, or they may be due to a displacement of the pacemaker within the sinus node before it passes to the a-v node. The first explanation is the correct one according to Lewis² when the P-R interval is decidedly less than

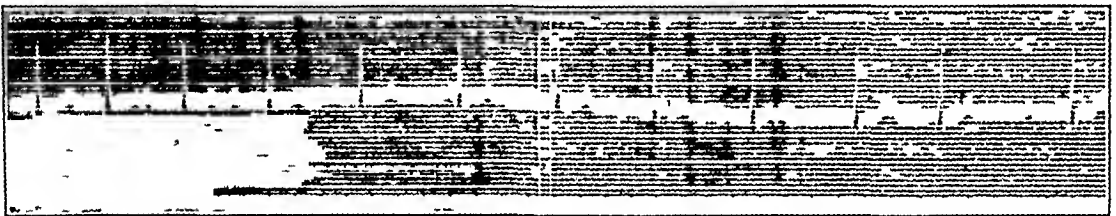


Fig 9—Case 3 Lead III. The P-R intervals of the earliest cycles are about 0.36 sec. From Cycle 5 to Cycle 10, inclusive, auricles and ventricles are contracting independently and the ventricles contract six times during this period while the auricles contract but five.

normal. This is true of the first three transitional beats of Figure 6. The last transitional beat of Figure 6 shows a slightly deformed P complex and a normal P-R interval so that it is possible that both these phenomena occur. Similar explanations may be offered for the fact that the inverted P complexes may vary considerably in size and form (Fig 5). This may be due either to the interference of two rhythms or to changes in the location of the pacemaker within the a-v node.

RHYTHMIC ESCAPE OF THE VENTRICLES WITH ATRIO-VENTRICULAR DISSOCIATION PRODUCED BY DEEP BREATHING

The dislocation of the pacemaker which occurred in Case 3 during forced respiration was somewhat different from that observed in Cases 1 and 2. Figure 9 shows the effect of forced respiration on the heart mechanism in this case. The patient had a slight degree of heart block. The P-R interval was so long that P fell on T of the ventricular complex of the previous cycle when the heart was beating at its usual rate. At the beginning of expiratory slowing P

and T gradually separate (Fig 9), but the P-R interval remains the same. After the fourth cycle of Figure 9, however, the P-R interval gradually becomes less and less until in the seventh cycle P falls on R. P then appears between R and T and finally falls on T in the tenth cycle. Thereafter the P-R interval is the same as at the beginning of the figure. Between Cycle 4 and Cycle 11, auricles and ventricles contracted independently. During the period of dissociation the ventricles were contracting more rapidly than the auricles and this difference in rate was so marked that the ventricles contracted six times while the auricles contracted only five. We are therefore dealing with the escape of a center located low down in the junctional tissues as the result of expiratory slowing of the sinus rhythm. The failure of the auricles to respond to the lower center was probably due to the heart block present. That short periods of dissociation may result when the idioventricular rhythm escapes as a result of sinus slowing even when there is no heart block is shown by Figure 7. This curve was obtained from Case 1. The P and R complexes of the first two cycles after slowing began are partially coincident. The P complexes are upright and so far as can be told are of the same form as those immediately following them. These characteristics indicate that the contractions which gave rise to these complexes were of sinus origin. The marked shortening of the P-R intervals makes it certain, however, that the ventricles responded to the junctional tissues. The dissociation of auricles and ventricles in this instance is due to the fact the stimulus from the center in the junctional tissues did not reach the auricles until they had become refractory.

In each of the cases described in this article, a-v rhythm could, at certain times, be produced at will by deep respiration. So far as we know, no similar cases have previously been reported. The production of a-v rhythm in man by deep breathing is analogous to the production of a-v rhythm in animals by stimulation of the vagus. In the clinical cases, however, in contrast to the experimental, the production of a-v rhythm is aided by a pathologic increase in the inherent rate of some center in the junctional tissues.

SUMMARY

Three cases are reported showing changes in the location of the pacemaker associated with deep respirations. These changes may be divided into three classes:

- 1 Migration of the pacemaker within the sinus node, or within its immediate neighborhood.

- 2 Migration of the pacemaker from the sinus node to the a-v node. The transitions from the normal rhythm to the a-v rhythm and

vice versa were sometimes abrupt, but at other times transitional beats occurred which were probably due to interference phenomena

3 Escape of the idioventricular rhythm with complete atrioventricular dissociation, during which the ventricles contracted more rapidly than the auricles This occurred both in a case in which there was a slight degree of heart block and in a case in which this complication was not present

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THE SYMPTOMS OF URINOD POISONING*

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I INTRODUCTION

The study of the toxic nature of urine has interested investigators for many years. The continued attraction which this subject affords is no doubt due to the part which urinary retention plays in the vital economy. When it occurs it may produce only headache and a general malaise, yet it cuts down the efficiency to a marked degree. In severer cases it may lead to grave symptoms and even death.

In attempting to account for this poisoning investigators have more often attributed it to a single urinary constituent. But a few have concluded that it was due to a number of substances.

In the study of a new substance¹ which is found in all urines, it was noticed that this substance, called *urinod*, produced headache and malaise. This led to a more careful investigation of its toxic nature.

From experiments conducted thus far, *urinod* seems to be one of the most toxic substances in normal urine. It is thought, therefore, that it may account for some of the symptoms of uremia. It must be understood, however, that this study does not attempt to explain uremia by the aid of *urinod* alone, but merely to show that it may be a contributing factor.

II PREPARATION OF URINOD

Urine was treated with dilute sulphuric acid so as to make about 3 per cent concentration of acid. The mixture was permitted to stand several days, becoming darkly colored and giving off disagreeable odors. At this stage the urine was distilled and the distillates were extracted with ether.² Acids, phenols and bases were removed from the ether extract by shaking successively with aqueous solutions of sodium carbonate, sodium hydroxid and hydrochloric acid. The ether solution, containing neutral substances, was concentrated and then subjected to steam distillation to remove *urinod* from the less volatile substances.

The steam distillation gave a low boiling thio-compound, *urinod*, a high boiling compound and sulphur in the distillate. This distillate was extracted with ether. The ether extract was washed with solutions of sodium carbonate, sodium hydroxid, and hydrochloric acid to remove possible traces of acids, phenols and bases. The ether solution was then dried with calcium chlorid and shaken in a separating funnel with metallic mercury to remove sulphur. The ether solution was concentrated and finally distilled in vacuo.

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* From the laboratory of chemistry of the University of Washington and the laboratory of physiology of the Harvard Medical School

1 Dehn, W. M., and Hartman, Frank A. Jour. Am. Chem. Soc., 1914, xxxvi, 2136

2 For method of extraction see Dehn and Hartman, *loc. cit.*, Note 1, p. 2126

The first distillate up to about 100 C at 30 mm always contained oil, with an allyl mustard oil or ethyl xanthate odor. The middle fraction, boiling at 108 C, with 29 mm pressure, contained urinod, while the final fraction contained an oil boiling at 170 C with 29 mm pressure.

From the first seven hundred liters of distillate from 1,000 liters of urine 5 gm of urinod were obtained. Of course some was lost during the handling, acidulation, distillation, ether extraction, concentration, treatment with acids and alkalies, distillation with steam, reextraction, drying and distillation in vacuo. It has been estimated that urinod occurs to the extent of one to two parts in 100,000 parts of urine.

III PROPERTIES OF URINOD

The boiling point of urinod is 108 C. at 28 mm. It cannot be distilled at ordinary pressure without decomposition. Urinod does not solidify in an ordinary freezing mixture. It is a light yellow oil, slightly heavier than water. It is soluble in ordinary organic solvents, but is insoluble in water. It is very volatile with steam. It has a very penetrating, persistent, nauseating odor of urine. It is very toxic, as will be shown in the experiments to follow.

Urinod darkens rapidly in direct sunlight, reduces solutions of potassium permanganate and ammoniacal silver nitrate in the cold, reacts with Millon's reagent, but not with Fehling's reagent. With fixed alkalies the odor of urinod is changed to a terpene-like odor.

IV COMPOSITION³ AND STRUCTURE OF URINOD

The empirical formula of urinod has been established as C_6H_8O .

Urinod is insoluble in hot dilute solutions of hydrochloric and sulphuric acids, therefore it cannot contain a basic (or alcohol-oxygen or ether-oxygen) group.

Urinod is optically inactive, hence, if not a racemic mixture, it cannot contain an asymmetrical carbon atom.

Urinod reacts with bromin contained in carbon tetrabromid, giving a strong evolution of hydrogen bromid and a solid bromo-derivative; hence it is a *cyclic* compound. Additional evidence of its cyclic nature is obtained from the formation of a dinitro-derivative (golden needles melting at 78 C) by treatment with cold, dilute nitric acid.

Urinod reacts with semicarbazide, forming a compound melting at 254 C. Therefore it is either a *ketone* or an *aldehyde*.

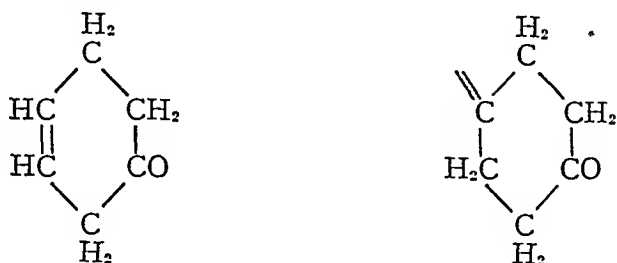
Urinod reacts with hydroxylamin, phenylhydrazin and hydrogen sulphid, forming derivatives not possessing the characteristic odor of urinod. These compounds indicate the presence of a *carbonyl* group in urinod.

The oxidation of urinod by ammoniacal silver nitrate, also by aqueous solutions of potassium permanganate, indicates close relationship with hydrobenzene derivatives.

3 Dehn and Hartman, *loc cit*, Note 1, p 2138

No known compounds having the same empirical formula as urinod possess the same properties

From the foregoing considerations and other considerations, discussed in a paper⁴ previously published, two possible structural formulas have been obtained



That urinod may possess the second formula gathers support from consideration of its characteristic toxic properties and its odor—the isocyanids and other bivalent⁵ carbon compounds being both toxic and malodorous

V URINOD OCCURS IN THE CONJUGATED FORM

That urinod does not occur free in fresh, normal urine is concluded from consideration of the following evidence

- 1 The odor of urinod is absent from fresh urine
- 2 Hydrolysis by fermentation or chemicals develops composite odors containing the odor of urinod
- 3 Urinod is very toxic, therefore for physiological reasons it must be rendered harmless by conjugation
- 4 Although urinod is easily volatile with steam, each fraction of the distillate from urine and even the heated residue gives off the odor of urinod, hence not only is its formation by hydrolysis difficult, but, *a priori*, it must exist in the conjugated form
- 5 Additional support is given to this conclusion from a consideration of the many other conjugated substances in the urine

VI METHODS OF ADMINISTERING URINOD

At the beginning of the experimental work with urinod, a method of injection was sought. But for the reason that solvents for urinod are more or less harmful to the body tissues, this method was thought to be rather unsatisfactory

In a few cases the pure oil was injected intramuscularly, intravenously or subcutaneously. The use of a syringe was found to be too wasteful because of the oil adhering to it, therefore in the cases

4 For more detailed discussion see Dehn and Hartman, *loc cit*, p 2141

5 Nef *Ann d Chem* (Liebig's), 1894, cclxxx, 303, 1895, cclxxxvii, 274, 1897, ccxcviii, 202. Wade *Jour Chem Soc*, 1902, lxxx, 1596. Lawrie *Am Chem Jour*, 1906, xxxvi, 487

of intramuscular and subcutaneous administration the urinod was dropped from an ampoule into an incision in the muscle or skin

The method used most often in animal experimentation was to drop the urinod into the pharynx. The capillary tube of a weighed ampoule of urinod was broken and the oil forced out by heat. The weight of the ampoule containing the remainder of the urinod together with its broken capillary, subtracted from the original weight, gave the amount of oil used.

In the two experiments on man in which urinod was taken intentionally, an open vial containing a drop of urinod was used. One nostril was held shut, the other was placed in contact with the opening of the vial, so that enough space was left for the inhalation of outside air. In this manner urinod vapor was mingled with the inspired air.

Because of the difficulty in obtaining urinod in any considerable quantity, the use of small animals was necessary in a majority of cases. In the following experiments something less than a total of 300 milligrams was used.

VII EXPERIMENTAL RESULTS

1 The frog—Urinod was quite toxic for frogs, one five-hundredth to one eight-hundredth of the body weight being sufficient to produce death in from twenty-five minutes to a few days, depending on the place of injection. Injections in the muscles of the hind leg were least effective, while doses by the mouth were quickest in their action. Death was due to the stopping of respiration.

A number of symptoms developed in the cases in which death did not take place for several hours. Twitchings and dyspnea were followed by convulsions and a high degree of irritability. In the last stages the animal became limp and would not respond to stimulation.

It is an important fact to be borne in mind that the heart was unaffected by urinod. The heart finally ceased beating, due to asphyxia. The reason that it continued so long after the lungs were inactive was no doubt due to respiration through the skin.

Tree frogs were used in the following experiments because of their small size.

A frog was given urinod by the mouth in the proportion of 1 part urinod to 460 parts body-weight. The frog jumped about a few times and then remained quiet. After 25 minutes the heart beat 100 times per minute, there were two or three jerky inspirations and then a long pause. After five minutes the animal was so weak that he could not sit up, breathing had practically stopped. After seven minutes he would kick very weakly when disturbed, he jerked and twitched much of the time. After ten minutes convulsions occurred. After thirteen minutes the heart had been reduced to 44 beats per minute, at this time tremors passed over the body. The heart continued beating for twelve minutes longer.

In this animal a condition of non-irritability had developed after ten minutes while death occurred in twenty-five minutes. The intermediate symptoms, such as twitchings and convulsions, were scarce and short-lived. Evidently more than the lethal dose had been given.

An examination of the esophagus and stomach showed that a large proportion of the urinod had not been absorbed. This is not surprising considering the insolubility of urinod in water.

B Another frog was given urinod in the proportion of 1 800 body weight, by dropping the oil into an incision in the abdominal wall. The frog was very frantic at first, jumping about and in various other ways showing his discomfort. After six minutes breathing had become slow and jerky. After sixteen minutes convulsions occurred, preceded by jerking and twitching, his legs were sprawled out and he was so weak that, although responding to very slight stimulation he could barely jerk. After thirty-six minutes the heart beat 72 times per minute, there was congestion of the blood vessels on the abdomen. After fifty minutes there was a quiet period interrupted by occasional jerks and twitches. After 175 hours, the heart beats were only reduced to 70 times per minute, the frog was no longer nervous, and breathing had become more spasmodic than ever. After three hours the heart beats were 56 per minute and twitching of individual muscles continued. After 45 hours the frog stopped breathing. At 55 hours after the administration of urinod the heart stopped beating.

This experiment demonstrates that although urinod is practically insoluble in water it is absorbed in sufficient quantity to affect the respiratory center. Very little, apparently, is necessary to cause dyspnea, as in six minutes this occurred, while it took four and one-half hours to carry enough of the poison to this center to stop its action completely.

As in the preceding case, very little of the urinod given was carried away.

The decrease in the rate of the heart beat is always in proportion to the decrease in the respiration and lags behind, as these experiments and those that follow demonstrate. Moreover, the fact that urinod has no direct action on the frog's heart was shown in another way. Excised frog-hearts were immersed in Ringer's solution, in which a drop of urinod had been placed. The rate of beat was then compared with other hearts in the same conditions except that urinod was absent. With ten trials no effect could be noticed even when urinod was brought in contact with the heart in the form of a large drop.

C In a third experiment⁶ urinod in the proportion of 1 2,500 body-weight had been injected into the muscles of the thigh of a frog. He immediately showed his irritation by jumping about. (These first effects were undoubtedly due partly to the mechanical irritation in making the incision.) After two minutes he jumped about very frantically, but his efforts were very weak. After three minutes he became very quiet, the injected leg had become paralyzed. After thirteen minutes he frequently gaped his mouth. After eighteen minutes the heart beat 59 times per minute and the muscles occasionally twitched. After twenty-one minutes there were convulsions. After twenty-three minutes his breathing had become irregular and he had become very frantic. This was followed seven minutes later by a state of nonirritability. After thirty-two minutes breathing had all but ceased, muscular twitchings and heart beats being the only indications of life for a time. After thirty-five minutes there were six respirations in one minute, first a single respiration, then a pause of forty seconds, followed by 5 respirations in as many seconds, another pause then a few more respirations followed. The injected leg was by this time congested with blood. Judging by previous experiments, it was thought that these symptoms were ushering in the end. After seventy minutes, however,

6 It is worth while to call attention to the similarity of urinod poisoning to carvone poisoning, as carvone can be easily obtained, while urinod is obtained only after considerable time and labor. The chemical structures and physical properties of the two substances are somewhat similar. Carvone is an unsaturated cyclic ketone with a penetrating odor. It is insoluble in water. Although not so toxic as urinod, carvone produces death in the same manner by injury to the respiratory center. The heart stops beating only after asphyxiation. The preliminary symptoms are twitching and dyspnea, while in grave cases convulsions and conditions of non-irritability follow. These effects were studied in the frog, the lizard and the mouse.

the frog began to recover. After two hours he had apparently recovered. In three days the injected leg was red and swollen to the tip of the toes, the frog had again become quite sick. He died during the third day.

In this experiment it was not positively known whether death was due primarily to urinod or to secondary causes. The last symptoms preceding death were a gradually increasing weakness, with an increasing condition of non-irritability.

2 *The lizard*—The animals used in these experiments did not belong to a very active species (*Gerrhonotus multicarinatus*).

The symptoms resulting from urinod poisoning resembled those present in the frog, except that there was considerable jerking of the body from side to side. Death was due to a checking of respiration. Urinod was administered orally in all cases.

A A lizard was given urinod in the proportion of 1 14,000 body-weight. After two minutes the lizard began to jerk his body and twitch his eyelids. Gradually the spasms increased in vigor and breathing became more difficult. In the course of an hour the jerks became weaker. After 15 hours the animal lay still except with an occasional twitching. He would not move when stimulated. During the course of three hours, however, this state of nonirritability had gradually passed away, the animal showing complete recovery.

This experiment demonstrates that in urinod poisoning the symptoms may become very severe, even so far as prolonged paralysis, yet they may be followed by complete recovery. As soon as absorption of the poison commences, detoxification probably begins. If urinod does not occur in sufficient quantity, enough of that being absorbed can be rendered harmless so that a fatal poisoning does not result.

B Urinod was given to another lizard in the proportion of 1 8,200 body-weight. In a little more than two minutes he began to twitch. The twitches gradually grew into jerks. After four minutes he crawled about slowly, jerking continually. After seven minutes he was so frantic that he darted first one way and then the other. After twenty minutes the ability to crawl had been lost, although there was continued jerking from side to side and twitching of the individual muscles. When placed on his back the lizard could not turn over. In the course of three hours he began to regain the use of his limbs. After four hours he had gained enough to right himself when placed on his back. However, he still continued to jerk. After nine hours he had recovered.

This experiment corroborates the results of the preceding one.

C In a third experiment the dose of urinod was increased in order to study the symptoms leading up to death. One part urinod to 1,800 parts body-weight, was given. After the poison began to affect him the symptoms became very severe in a short time.

At six minutes he had begun to twitch, while in ten minutes the eyes were half shut and he was unable to crawl. He gradually grew weaker until at one hour from the time of administering urinod, the feet were sprawled out with the soles up. After 1 25 hours, the state of nonirritability was complete, twitching being the only sign of life. Death occurred 15 hours after urinod was given.

D In the fourth case the dose of urinod was slightly increased beyond that used in the previous experiment.

Twitching of the eyelids followed a few seconds after administration. Spasms and paroxysmal breathing soon ensued. After ten minutes the limbs were so weak that they could not support the body. At the end of fifteen minutes an oily excretion was defecated⁷. This contained a large amount of urinod. By this time the eyes of the lizard were kept half closed and when picked up the

7 A lizard which was given a lethal dose of the oil carvone excreted a great deal of it six minutes afterward by the intestinal path.

animal was limp. In thirty-five minutes movement was reduced to occasional twitchings. Death occurred one hour after administering urinod.

Autopsies of animals killed by urinod have always shown a large amount of the poisonous oil in the stomach and intestines. Apparently there was always an attempt to remove the urinod by the intestinal path. In this experiment a considerable amount of the oil administered was removed from the body in this manner, but enough remained to kill. That death does not occur very rapidly, as with many soluble poisons, is undoubtedly because urinod is absorbed so slowly.

3 The mouse—It was desirable to study the severer symptoms of urinod poisoning in mammals. Therefore, on account of the small amount of the poison required to produce these results, the mouse was used.

A mouse weighing 109 gm. was given urinod at intervals of a few hours to a few days, a drop being placed on the tongue.

First dose 142 mg. (Ratio 1:767 body-weight). The mouse immediately rubbed his snout on the floor of his cage, causing the oil to run out of his mouth. After two minutes he opened and closed his eyes, and then kept them half shut. After three minutes he jumped and twitched. After six minutes slow and difficult breathing developed. After ten minutes he ran about frantically. After twelve minutes he lay as though in a stupor. After fifteen minutes his eyes were open again. After seventeen minutes he ran about chewing things but not eating. In one hour his symptoms became milder. After two hours he twitched his ears continually. After three hours his body still twitched and he did not move even when stimulated in a manner which had previously provoked a response. After thirteen hours he trembled a great deal, his appearance was depressed.

He twitched for twenty-four hours with eyes half shut and breathing labored, he also seemed to be chilly. A few hours after the administration of urinod the fur became so moist from perspiration that the hair was matted as though it had been immersed in water.

Second dose Six days after the first dose, the same mouse was given 82 mg. of urinod (1:1,329 body-weight). The symptoms, as described above, with little variation, again appeared.

Third dose Eight minutes after the second dose, 103 mg. of urinod was given. In four minutes the mouse's eyes were completely shut, he twitched spasmodically. After six minutes he blinked his eyes. After eight minutes he ran frantically back and forth, occasionally rubbing his snout on the cage, his breathing was slow and irregular. After twenty-two minutes he was breathing rapidly again but irregularly, he also jerked his body. At thirty-two minutes there was a slight spasm. At thirty-seven minutes there was another slight spasm. After forty-two minutes he was frantic and possessed a high degree of irritability. After forty-seven minutes he was so irritable that he jumped at the slightest disturbance. At sixty minutes he had convulsions, then intervals of frantic running about with periods of quiet between them continued for several minutes. After nine hours he still trembled.

Fourth dose Seven days after the first dose, 3 mg. of urinod was given. The mouse became nervous and twitched. This was followed by a period of quiet.

Fifth dose Thirteen days after the first dose a drop of urinod was given at intervals during the course of thirty minutes until 60 mg. had been taken (Ratio 1:182). In twenty minutes after the first drop was given the breathing was slow and difficult, the eyes were half shut and the mouse paid no attention to noises. After twenty-seven minutes the eyes were closed and the breathing was not only slow, but very irregular, first, there was a labored respiration, then two or three respirations followed rapidly. At twenty-eight minutes his head sank to the floor and his body jerked. After thirty-seven minutes he passed

into a state of nonirritability, breathing in paroxysms. At forty minutes he had a convulsion. At forty-five minutes convulsions again occurred. After one hour the breathing became more regular. After 35 hours the breathing was almost normal, but the body trembled. At 17.75 hours he was continually blinking his eyes, first one and then the other, there was also twitching of the ears. After nineteen hours he occasionally jerked. He kept up the blinking of his eyes until the end of the fourth day. In this movement he always lacked coordination as the eyes were blinking alternately instead of in unison. During this period he kept his eyes partly closed when not in the act of blinking. On the fifth day he had about regained his normal condition.

The symptoms developed in the mouse were muscular twitchings, heightened irritability, apparent drowsiness, labored paroxysmal breathing and dyspnea.

The same proportion of urinod was not as effective in the mouse as in the lizard for it was impossible to place the oil far enough into the throat to prevent removal to the floor of the cage.

4 *Man*—Although the graver symptoms of urinod poisoning cannot be determined experimentally in man, he serves as an excellent subject for the study of many minor symptoms.

It was while working with urinod in the laboratory that its toxic nature was discovered through the effect produced on breathing its vapors. This was noticed whether working with the pure substance or with the complex distillate from acid-treated urine.

One of the first effects noticed was the intense nausea produced when working over small amounts of urinod. This was almost invariably followed by headache and mental depression. The headache was often occipital in its location.

During periods when I was handling urinod every day for a number of days together, I noticed loss of appetite and a heaviness of the stomach after eating, also constant weariness and frequent periods of drowsiness. Sometimes there was considerable irritability of temper. Occasionally there were marked restlessness and insomnia, although these were usually followed by heavy sleep.

The breathing of urinod from a small vial for ten minutes caused a peculiar sensation in the head, followed by a numbness in the occipital region. It became impossible to concentrate the attention for a time. Headache and depression soon developed. These symptoms, together with irritability of temper lasted for about five days.

At various times when under the influence of urinod I noticed an unusual chilliness. During one period, about three days in length, after I had handled more urinod than usual, I felt a great desire to micturate several times at night although the bladder might be practically empty. The urine gave a burning sensation in its passage. Moreover during this period some itching of the skin occurred. It may be mentioned that after long exposure to urinod, fatigue developed very early upon exertion.

In distilling urinod on one occasion, the stopper to the flask being accidentally removed, I inhaled a considerable quantity of the vapor. In a few seconds I realized a very peculiar, indescribable sensation in both the lumbar and occipital regions, the latter predominating. Shortly after it took effect I felt extremely restless and irritable. This feeling gradually passed off into headache and depression which lasted for a few days.

It was interesting to note the effect of urinod on other individuals. Those who remained for a few minutes in the room where urinod was being used, complained of headache and depression.

One individual inhaled urinod from a vial for five minutes. An extremely nauseating sensation was experienced while breathing the urinod and for some time later. Headache began in a few minutes, with a tendency to sleep. The next day this person was extremely irritable. The effect passed away in about three days.

If one considers the minute trace of urinod which would be taken into the system by inhalation, one can realize how toxic the substance must be to produce the results described ⁸

An important characteristic of this toxic effect is the slowness with which it disappears

The symptoms commonly shown by urinod poisoning in man are, nausea, headache (more pronounced in the occipital region), mental depression, loss of appetite, heaviness of stomach after meals, constant weariness and drowsiness. The symptoms occasionally developed are, irritability of temper, marked restlessness, insomnia, inability to concentrate the attention, chilliness and desire for frequent micturition

VIII THE LETHAL DOSE OF URINOD

The quantity⁹ of urinod necessary to produce the graver symptoms, or even death, is very small, judging from the experiments on animals

The amount given them was small, but the portion actually absorbed or carried away by the circulation was very minute, as shown by the quantity remaining unabsorbed. In postmortem examination, urinod given by the mouth is largely recovered in the stomach and intestines, while that injected intramuscularly or subcutaneously is found little diminished in that region

From these facts it is very certain that amounts considerably smaller than 1 part to 800 parts body-weight (frog) would produce death if it were all absorbed in the circulation. Moreover, if other substances that are normally eliminated by the kidneys, accumulated in the blood, the resistance of the tissues would probably be diminished¹⁰. It is also quite possible that there is an increase in urinod under certain conditions

8 Later experiments have shown that when all of the inhaled air is made to pass over urinod in the following apparatus only 28 mg are volatilized in thirty minutes. The following arrangement was used. A liter bottle was supplied with dry air from a tower of CaCl_2 and soda lime. A short wide-mouthed vial, containing a weighed quantity of urinod, was supported so that the urinod was about 0.5 cm below the opening of the exit tube of the bottle. This exit tube was connected with a piece of rubber tubing. The rubber tubing fits closely in one nostril, the other being held shut during inspiration. At expiration the rubber tube was pinched to prevent any back flow of air. In this way the amount of urinod used could be accurately determined.

9 It has been found recently that by dissolving urinod in olive oil it is more toxic when injected subcutaneously. When given thus, one part of urinod to 3,000 parts body-weight is sufficient to kill mice, even then only about one-half to one-third of the oil is absorbed.

10 Cawadias, Alexandre (*Compt rend Soc de biol*, 1910, lxi, 153) working with blood serum of uremic patients adopted the hypothesis that a physico-chemical modification of the colloids in the serum made an increase in the toxicity of substances accumulating in uremia—the accumulation of potassium salts, ammonium carbonate and urea played a part in this modification of the colloids.

IX INDICATIONS OF URINOD RETENTION IN THE BODY

Because of the effect which it might have, on account of its toxic nature, it is of interest to note the indications of urinod-retention in the body. Urinod gives the characteristic odor to urine, therefore its presence is recognizable from its odor. Also, urinod is a normal constituent of all urines. If at any time urine does not have an odor, from the above considerations it would be concluded that urinod had been retained in the body. The odor of urine is said to be absent in some cases of uremia,¹¹ therefore, in those cases urinod is probably retained in the body.

Positive evidence of urinod retention is obtained from the fact that the skin and breath of uremic patients are often described as having a urinous odor.¹² This observation and the following would indicate that not only was urinod retained but that it was present in the free condition, as it is the unconjugated substance which gives the urinous odor.

Christison's¹³ observation is very important in its bearing on this point. He found the odor of urine in the heart blood of a man who had died of uremia. Two ounces of blood were removed with great care from the heart so that contamination was impossible. This blood was shaken with alcohol and filtered. Following this it was carefully evaporated to dryness on a vapor bath. The residue was then treated with HNO_3 , giving the odor that is obtained when urine is treated with HNO_3 .

X A COMPARISON OF URINOD SYMPTOMS WITH UREMIC SYMPTOMS

The symptoms of urinod poisoning, as shown in the foregoing experiments, are headache, nausea, loss of appetite, heaviness of the stomach after meals, twitching, irritability of temper, mental dulness, physical weariness, drowsiness, dyspnea, convulsions and a condition of nonirritability. Occasionally there are other symptoms such as restlessness, insomnia, itching of the skin, frequent micturition, chilliness and fatigue after slight exertion.

Tyson¹⁴ says that a frequent desire to micturate is an early symptom of uremia. In regard to the symptom of chilliness, that was described by Saundby.¹⁵ Fatigue after slight exertion was observed in a case of uremia by Foster.¹⁶ All of the other symptoms of urinod

11 de Beauvais, M. *Compt rend Acad d sc*, 1850, xlvii, 641

12 Willson. *Jour Am Med Assn*, 1905, xlv, 23, Porter, W H. *Renal Diseases*, 1887, p 84, Christison, R. *Granular Degeneration of the Kidneys*, 1839, p 202

13 Christison, R. *Granular Degeneration of the Kidneys*, 1839, p 169

14 Tyson, James. *Bright's Disease and Diabetes*, 1881, p 103

15 Saundby, Robert. *Lectures on Renal and Urinary Diseases*, 1896, p 158

16 Foster, N B. *THE ARCHIVES INT MED*, 1913, xii, 455

poisoning are often present in uremia¹⁷ with one exception, and that is the paralysis of the center which coordinates the movement of the eyelids (observed in one instance in the mouse) So far I have not found a description of this symptom in uremia

An important organ which is affected in uremia is the heart Urinod has no effect on this so far as experiments up to this time have shown The changes in blood pressure which sometimes are present in uremia apparently bear no relation to the retention of urinod, as it has been impossible to obtain any effect on blood pressure by the use of urinod

Apparently urinod plays no part, or at most very little, in the production of dropsy, as only in one instance was there any appearance of edema

Therefore it is concluded from the above considerations that the symptoms of urinod poisoning resemble very much the nervous symptoms of uremia It is possible, then, that urinod is the cause of some of the nervous symptoms present in uremia On the other hand, there are other substances in the urine which produce symptoms such as twitching, convulsions, and a condition of nonirritability and coma For this reason it is probable that these substances contribute to this effect on the nervous system A varying amount of these substances which influence the nervous system might account for the variations in uremic symptoms Obermayer and Popper¹⁸ thought that the changing clinical picture in uremia might be due to the changing power of elimination in the kidney for different substances

SUMMARY

1 Urinod¹⁹ is prepared from the distillates of acid-treated urines It is a neutral malodorous oil boiling at 108 C with 28 mm pressure It is a cyclic ketone with the empirical formula C_6H_8O

2 The symptoms produced by urinod ordinarily are nausea, headache, loss of appetite, heaviness of the stomach after meals, twitching, irritability of temper, mental dulness, physical weariness, drowsiness, dyspnea, convulsions and a state of nonirritability

3 Urinod appears to be one of the most toxic substances in urine

4 Cases are cited in which there have been indications of urinod retention in the body

5 The symptoms of urinod-poisoning resemble the nervous symptoms of uremia Urinod retention, therefore, might partly account for these nervous symptoms

17 Furbringer, Paul Diseases of the Kidneys, Trans by W H Gilbert, 1895, 1, 38, also Garrod, A E Osler's Modern Medicine, 1909, vi, 91

18 See Friedrich and Hugo Ztschr f klin Med, Berl, 1911, lxxii, 332

19 Further studies are being made on urinod

A STUDY OF THE SEVERAL FACTORS OF ACID EXCRETION IN NEPHRITIS *

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Recently acidosis in nephritis has attracted much attention among clinical investigators and many articles dealing with the subject have appeared. Considerable evidence has accumulated which leaves little doubt that in certain of the more severe types of chronic renal disease there occur mild grades of acidosis. The facts revealed in various researches which confirm the frequently observed clinical picture of acidosis in nephritis include lowered alveolar carbon dioxide tension, the decreased affinity of hemoglobin for oxygen, reduced alkalinity of the blood, increased intensity of urinary acidity (hydrogen ion concentration) and the retention of alkali by the body in cases in which the kidney is capable of the rapid elimination of an excess of alkali.¹

The purpose of the present communication is to present certain data on the acid excretion in nephritis which we have collected over a period of three years during our investigation of the process of acid excretion in health and disease.²

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1 Palmer, Walter W, and Henderson, Lawrence J. Clinical Studies on the Acid Base Equilibrium and the Nature of Acidosis, *THE ARCHIVES INT MED*, 1913, xii, 153, Sellards, Andrew W. The Essential Features of Acidosis and Their Occurrence in Chronic Renal Disease, *Bull Johns Hopkins Hosp*, 1914, xxv, 141, for a review of the literature on this subject

2 Henderson, Lawrence J, and Palmer, Walter W. The Intensity of Urinary Acidity in Normal and Pathological Conditions, *Jour Biol Chem*, 1913, xiii, 393, The Extremes of Variation of the Concentration of Ionized Hydrogen in Human Urine, *Jour Biol Chem*, 1913, xiv, 81, Newburgh, L H, Palmer, Walter W, and Henderson, Lawrence J. A Study of Hydrogen Ion Concentration of the Urine in Heart Disease, *THE ARCHIVES INT MED*, 1913, xii, 146, Palmer, Walter W, and Henderson, Lawrence J. Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, *THE ARCHIVES INT MED*, 1913, xii, 153, Henderson, Lawrence J, and Palmer, Walter W. The Several Factors of Acid Excretion, *Jour Biol Chem*, 1914, xvii, 305, Henderson, Lawrence J, Palmer, Walter W, and Newburgh, L H. The Swelling of Colloids and Hydrogen Ion Concentration, *Jour Pharm and Exper Therap*, 1914, v, 449

I MATERIAL AND TECHNIC

Our observations include the study of fifty-eight cases of varying grades of nephritis for a total of 377 days. As in our studies on normal individuals, we have determined for the twenty-four hour amount of urine the hydrogen ion concentration, acid excretion and ammonia excretion in all cases.

In eleven of the subjects, however, the urinary nitrogen and non-coagulable nitrogen in the blood are added to the observations. Certain other facts of clinical interest, such as phenolsulphonephthalein excretion, blood pressure, specific gravity, albumin and the microscopical examination of the urinary sediment, are also included among the data. We have made no attempt to carry out elaborate studies in metabolism, although recognizing the value of such a procedure, but have, anticipating criticism, studied the effect of diet on the acid factors of the urine in two normal individuals, using the same articles of food which all the cases we report received while under observation. The study of the effect of diet in the two normal subjects is divided into three periods. In the first period a low protein diet was obtained by the use of soluble arrowroot starch as a principle article of food, while in the second period we employed essentially the hospital "nephritic diet." The high nitrogen in the third period was secured by the ingestion of large quantities of milk and eggs.

The methods of study are the same as those described in our earlier papers. Urinary nitrogen and noncoagulable nitrogen in the blood were determined according to the methods of Folin³. All observations were made in duplicate. It may not be out of place here to call attention to certain precautions necessary in the study of acid excretion. First, it is highly desirable, in fact very necessary, to have a special nurse to control the diet and insure proper collection of the urine. An approximately standard diet should be used in all cases, in order to permit reliable comparisons. For a diet varying markedly from the one used in our work (Table 1) normal controls should be secured. Blatherwick⁴ and others have shown that by proper selection of diet in reference to the acid or basic nature of its ash, the acid factors of the urine may be markedly influenced.

Such extremes in diet practically amount to the feeding of acid or alkali, experiments with which we have already reported.

It is absolutely essential that the urine be collected in clean receptacles and well preserved. We have found chloroform with 5 per cent

3 Folin and Farmer Jour Biol Chem, 1912, xi, 493, Folin and Denis Jour Biol Chem, 1912, xi, 527

4 Blatherwick, N. R. The Specific Rôle of Foods in Relation to the Composition of the Urine, THE ARCHIVES INT MED, 1914, xiv, 409

thymol, 10 c c to a five-pint bottle, to be quite satisfactory During the collection of the twenty-four hour amount, the bottle should be kept well stoppered in a cool place, preferably in an ice chest, or if this be not practical, the bottle must be vigorously shaken after the

TABLE 1—NORMAL SUBJECTS, VARYING AMOUNTS OF PROTEIN
W W P

Vol ume, c c	Hydro- gen Ion Concen- tration	Acid N/10 c c	Am monia, N/10 c c	Acid + Am- monia	Acid - Am- monia	Am- monia N, Gm	Total Nitro- gen, Gm	Am- monia Nitro- gen Ratio	Diet
1,720	5.9	232	395	627	0.59	0.55	10.3	5.3	Soluble starch, cream, sugar, fruit, potato, butter, let- tuce
2,085	6.2	196	373	569	0.53	0.52	8.9	5.9	
1,405	6.0	258	302	560	0.85	0.42	6.6	6.4	
1,300	5.7	276	320	596	0.86	0.45	6.2	7.3	
2,349	5.7	392	560	952	0.70	0.76	16.0	4.8	Fruit, cereals, bread and but- ter, cream, sugar, eggs, potato, macaroni, milk, cheese
1,687	5.5	451	475	926	0.95	0.67	14.0	4.8	
935	5.4	475	503	978	0.95	0.70	10.8	6.5	
1,005	5.5	345	434	779	0.80	0.61	10.6	5.7	
2,105	6.0	370	595	965	0.62	0.84	20.4	4.1	Same as in Period 2 ex- cept marked increase in eggs
2,197	5.7	495	654	1,149	0.76	0.92	22.0	4.2	
2,088	5.3	720	785	1,505	0.92	1.10	24.9	4.4	
1,652	5.3	760	842	1,602	0.90	1.18	23.2	5.1	

Average acid ammonia ratio is 0.785

J H M

1,310	5.4	257	320	577	0.80	0.45	8.7	5.2	Same as in Subject W W P
2,447	6.1	191	275	466	0.70	0.39	7.0	5.6	
1,545	6.0	181	236	417	0.77	0.33	5.4	6.1	
1,460	6.3	139	245	384	0.57	0.34	4.5	7.5	
2,013	5.5	300	370	670	0.81	0.52	12.0	4.3	Same as in Subject W W P
945	5.7	316	332	648	0.95	0.47	9.1	5.2	
993	5.7	330	336	666	0.98	0.47	9.8	4.8	
1,322	5.6	303	360	663	0.84	0.51	9.4	5.4	
1,600	6.2	298	440	738	0.68	0.62	13.9	4.5	Same as in Subject W W P
2,138	5.9	368	457	825	0.81	0.68	17.2	4.0	
1,925	5.4	595	660	1,255	0.90	0.93	20.5	4.5	
1,462	5.3	535	716	1,251	0.75	1.00	17.2	5.8	

Average acid ammonia ratio is 0.797

addition of each single specimen The acid factors should be deter-
mined soon after the completion of the twenty-four hour amount
Especial care should be taken to exclude alkalis or acids from all
drugs used, not only during the observations but for some time before
starting the experiment

Subjects with infections of the genito-urinary tract are wholly unsuitable because of the activity of bacteria in changing rapidly and markedly the relations between acid and ammonia, as well as the hydrogen ion concentration of the urine. Female patients are less satisfactory than males because of the frequency of cystitis and the difficulty in securing uncontaminated specimens. However, with the divided bed pan devised by Dr. Denis of the Massachusetts General Hospital chemical laboratory, satisfactory collections may be made.

II CONTROLS

The experiments on the two normal subjects, W W P and J H M, were so planned as not only to include the usual variation in diet which might occur in the pathological cases, but also the unusual extremes of high and low protein intake, while using in the two cases, as far as possible, the same relative amounts of the different articles of food. The results of these experiments may serve as a standard for comparison of the normal with the pathological. Both individuals give results so nearly identical that what is said of one is also true of the other. The range of hydrogen ion concentration is between 6.3 and 5.3, varying roughly with the protein intake, the average for W W P being 5.7, for J H M 5.8, values which are slightly higher than the one of 5.98 previously reported. As might be expected, the amounts of acid and ammonia increase considerably with the increase in protein. For this reason they can not fairly be compared to our earlier normal values, but otherwise call for little comment. Our chief interest lies in the behavior of the acid-ammonia ratio designated as R in our earlier papers. This ratio varies considerably in the two individuals but never exceeds 1.00, the average for the twelve days in W W P being 0.785, with a range of 0.53 to 0.95, in J H M 0.797, varying between 0.57 and 0.98, average values only slightly higher than the one of 0.75 found in normal individuals on a mixed diet.

A quite remarkably close agreement on same days is found in the ammonia-nitrogen ratio which varies between 7.5 on the low protein days to 4.0 when the protein intake is high. On one day only is there a marked discrepancy, in which W W P has a ratio of 6.5 as against 4.8 in J H M. This close agreement between the two individuals is due unquestionably to the uniformity in amounts and articles of food.

III RESULTS IN NEPHRITIS

In Table 2 we have assembled the cases of nephritis in order of the value of the ratio between acid and ammonia. The general average of all the observations of the individual cases is given in the table.

because with the exception of Cases 4, 6, 20, 41, 43, 47 and 51, which have been added since, the detailed records of the acid factors appear in an earlier paper⁵ Identification of the cases in the earlier paper can be made by comparing the acid-ammonia ratio of the two tables

In a few cases we were unable to obtain a full twenty-four hour amount of urine, but as the loss was relatively small, the ratio between acid and ammonia was determined These cases together with other clinical data appear in Table 3

Table 4 contains the general averages with the maximum and minimum variations as well as the normal average previously reported

The total nitrogen in the urine was determined in Cases 4, 5, 6, 8, 18, 19, 20, 41, 43, 47 and 51, making it possible to compare the acid-ammonia ratio with the ammonia-nitrogen ratio in the urine To this data we have added the noncoagulable nitrogen in the blood and collected the whole in Table 5

Unfortunately only six of the cases studied in our series came to necropsy The acid-ammonia ratio, clinical and anatomical diagnosis in these cases, are brought together in Table 6

DISCUSSION

During the past few years there has appeared so much literature (much of which contains extensive reviews and bibliographies) dealing with "tests" of renal function, their value and significance, that any review of the subject here would be superfluous A satisfactory survey of this general field is to be found in the publication of Blum⁶ while the excretion of phenolsulphonephthalein, sodium chlorid, lactose, potassium iodid and water has been discussed by Fitz⁷ Since the appearance of Folin's method for the accurate and rapid determination of the noncoagulable nitrogen in small amounts of blood, several papers have been published on the value of increase in blood nitrogen as an aid in diagnosis and prognosis in renal disease Recent publications with references to the work on this subject are those of Tileston and Comfort,⁸ and Frothingham and Smillie⁹ Phenolsulphonephthalein

5 Henderson, L J, and Palmer, W W On the Several Factors of Acid Excretion in Nephritis, *Jour Biol Chem*, 1915, **xxi**, 37

6 Blum, Victor *Nieren physiologie und funktionelle Nierendiagnostik*, Leipzig, 1913

7 Fitz, R The Value of Tests for Renal Function in Early and Advanced Bright's Disease, *Am Jour Med Sc*, 1914, **cxlvi**, 330

8 Tileston, Wilder, and Comfort, C W The Total Non-Protein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Methods, *THE ARCHIVES INT MED*, 1914, **xiv**, 620

9 Frothingham, Jr, Channing, and Smillie, Wilson G The Relation Between the Phenolsulphonephthalein Excretion in the Urine and the Non-protein Nitrogen Content of the Blood in Human Cases, *THE ARCHIVES INT MED*, 1914, **xiv**, 541

TABLE 2—DATA OF AUTHORS' CASES ASSEMBLED

Case No	Sex	Age	Clinical Diagnosis	Systolic Blood Pressure, mm Hg	Urine			
					Phenol sulphone-phthalein % in 2 Hrs	Sp Gr	Albumin	Microscopical
1	M	36	Chronic nephritis	190	Trace	1 012	T	No casts Few W B
2	M	42	Chronic nephritis albuminuric retinitis	180	Trace	1 017	S T	Occasional hyaline casts with fat adherent R B C
3	M	47	Chronic glomerulonephritis	150	32	1 010	S T	Rare hyaline cast Many R B C
4	M	18	Chronic glomerulonephritis, albuminuric retinitis	180		1 010	L T	Few granular casts, few adherent R B C
5	M	22	Chronic glomerulonephritis, albuminuric retinitis	250		1 015	T	Occasional granular casts W B C
6	M	33	Chronic glomerulonephritis, albuminuric retinitis	220	5	1 012	T	Many granular, a few fatty casts
7	M	74	Arteriosclerosis (renal)	205	15	1 018	T	Many hyaline and granular casts W B C
8	M	48	Acute nephritis	170	33	1 015	T	Granular and hyaline casts Many R B C
9	M	61	Chronic glomerulonephritis, albuminuric retinitis	230		1 012	S T	Granular and fatty casts Many W B C
10	M	17	Chronic glomerulonephritis	155	63	1 015	L T	Many granular and fatty casts R B C W B C Few hyaline casts
11	M	33	Acute nephritis	160	40	1 010	S T	Hyaline and granular casts Many R B C
12	M	45	Chronic glomerulonephritis, albuminuric retinitis	250	Trace	1 015	T	Hyaline and granular casts
13	M	29	Chronic glomerulonephritis, albuminuric retinitis	200	11	1 010	S T	Rare granular casts
14	M	32	Nephritis (syphilitic), cirrhosis of the liver	140	51	1 020	T	Many granular casts few R B C
15	M	29	Chronic glomerulonephritis, albuminuric retinitis	210	5	1 012	T	Many granular, few hyaline casts Few R B C
16	F	32	Chronic glomerulonephritis	175		1 016	L T	Hyaline and granular casts R B C, W B C

—IN ORDER OF RATIO BETWEEN ACID AND AMMONIA

Urine							Remarks
Num-ber of Observations	Amount c c in 24 Hours	Acid Factors					
		Hydro-gen Ion Concen-tration	Acid N/10 c c	Am-monias N/10 c c	Acid + Am-monias	Acid - Am-monias	
4	1,094	5 3	217	55	272	3 95	Scarlet fever followed by nephritis when young Hyper-trophied heart Moderate edema Chronic uremia Died five months after leaving the hospital
5	1,365	5 6	196	59	255	3 33	Scarlet fever when young Nine weeks with edema Two weeks uremic Dyspnea Died
2	1,770	5 7	297	108	405	2 95	Frontal sinus at 35 For seven or eight years attacks of hematuria with mild uremia Left hospital feeling better of one of these attacks
7	2,280	5 5	350	118	468	2 97	For three weeks failing vision and puffy eyelids Devel-oped marked uremia, convulsions relieved by usual measures Discharged from the hospital without symptoms save poor vision
2	1,980	5 0	274	100	374	2 74	Etiology not clear For six months increasing symp-toms of uremia Failing vision At onset, edema Died four days after observations
4	900	5 0	194	75	269	2 60	Tonsillitis three years ago Moderate alcohol Mild uremic symptoms for six months For two weeks failing vision, dyspnea and slight edema of eyelids Cardiac hypertrophy, arteriosclerosis Left hospital without symptoms
2	1,346	5 0	265	128	393	2 07	A painter, lead colic twenty years ago For a year increasing dyspnea and uremic symptoms Cheyne-Stokes respiration Cardiac hypertrophy, marked arteriosclerosis, edema of legs Died two weeks after observations
5	1,548	5 1	395	204	599	1 94	Alcoholic Acute coryza for a week, associated with mild edema Slight cardiac hypertrophy, palpable arteries Improved
4	1,131	5 9	144	75	219	1 93	Increasing uremia for six months Dyspnea Hyper-trophy of heart, arteriosclerosis Died one week after observations Necropsy, arteriosclerosis
9	1,189	4 9	316	168	484	1 89	Etiology obscure Varying degrees of edema for six months Slight uremia Nonprotein nitrogen in blood 90 mg per 100 c c Much improved Died three months after leaving hospital
5	2,571	5 1	307	165	472	1 86	Alcoholic Hematuria and edema for two weeks Im-proved
5	912	5 1	193	107	300	1 80	Alcoholic Scarlet fever and frequent sore throat Dyspnea for a year Uremia for five weeks Left hospital against advice, moribund three days after observations Hypertrophy of heart Died shortly after leaving hospital
18	2,640	5 2	472	275	747	1 72	Tonsillitis six years ago One year mild uremic symp-toms Hypertrophied heart No marked arterio-sclerosis Only slightly improved Died one year later Chronic interstitial nephritis
19	868	5 2	318	195	513	1 63	Syphilis Positive Wassermann Three months with ascites and mild uremia Slight hypertrophy of heart Cirrhosis of liver Slight improvement
10	1,478	5 1	318	196	514	1 62	Nine years ago appendix abscess drained Eight years ago albumin found in urine No symptoms until three months ago, mild uremia Some improvement Died shortly after leaving the hospital
4	1,930	5 4	217	137	354	1 58	Alcohol and lead (water) Uremia for a year Convul-sions preceding entrance to hospital in a comatose condition Hypertrophy of heart Mild arteriosclero-sis Improved Died eight months later

TABLE 2—DATA OF AUTHORS' CASES ASSEMBLED IN—

Case No	Sex	Age	Clinical Diagnosis	Sys tolic Blood Pressure, mm Hg	Urine			
					Phenol sulphone phthalein % in 24 Hrs	Sp Gr	Albumin	Microscopical
17	M	43	Chronic glomerulo	220	20	1 015	T	Rare hyaline cast
18	M	43	Chronic interstitial arteriosclerosis, albuminuric retinitis	245	5	1 010	T	Many hyaline and granular casts
19	M	38	Chronic glomerulo	140	50	1 015	V S T	Many coarse granular casts, few hyaline casts Rare R B C
20	M	26	Chronic glomerulo, albuminuric retinitis	200	32	1 012	S T	Few hyaline and granular casts
21	M	61	Chronic interstitial	230	15	1 020	S T	Numerous granular casts W B C
22	M	57	Chronic nephritis	170		1 013	T	Fatty and granular casts R B C, W B C
23	M	15	Chronic glomerulo	160	70	1 024	V S T	Few hyaline and granular casts Many R B C Many W B C
24	M	63	Cardiorenal disease	220	Trace	1 010	V S T	Many granular casts
25	F	53	Cardiorenal disease, albuminuric retinitis	200		1 012	S P T	Nothing seen in sediment
26	M	36	Subacute glomerulo	150		1 018	L T	Many epithelial casts Few R B C
27	M	29	Subacute glomerulo	150		1 030	L T	Many fatty casts W B C
28	M	48	Chronic glomerulo, albuminuric retinitis	235	48	1 015	0	Rare hyaline and granular casts
29	M	19	Chronic glomerulo	170		1 015	T	Many hyaline and granular casts W B C
30	M	30	Nephritis (arteriosclerotic?)	140	40	1 025	T	Occasional hyaline cast W B C
31	M	20	Chronic glomerula	130	30	1 030	T	Many fatty casts R B C, W B C
32	M	15	Subacute Nephritis	110	55	1 030	L T	Many granular and fatty casts W B C
33	M	19	Subacute glomerulo	125	31	1 018	L T	Many granular casts Many R B C Some W B C
34	M	41	Cardiorenal disease, chronic glomerulo, albuminuric retinitis	170	Trace	1 015	S T	Few hyaline casts W B C
35	M	37	Chronic nephritis	130	40	1 013	V S T	Few hyaline and granular casts W B C

—ORDER OF RATIO BETWEEN ACID AND AMMONIA—(Continued)

Urine							Remarks
Num ber of Obs ervations	Amount c c in 24 Hours	Acid Factors					
		Hydro gen ion Concen tration	Acid N/10 c c	Am monia N/10 c c	Acid + Am monia	Acid + Am monia	
3	1,005	5.9	282	193	475	1.46	Mild uremia for several months. Big heart and some arteriosclerosis. No improvement. Died four months after leaving hospital.
2	3,710	5.0	463	322	785	1.44	Moderate alcohol. Wassermann suspicious. For three months, increasing dyspnea and uremia. Hypertrophy of heart, arteriosclerosis. Slight edema. Left against advice, died one week later.
5	1,534	4.9	430	348	778	1.24	Alcoholic. Septic arm three years ago, no albumin in urine then, eight days acute coryza followed by edema. No uremia. Heart enlarged. Left hospital improved.
4	2,321	5.2	399	330	729	1.21	Etiology obscure, eight weeks of mild uremia which increased. Died three weeks after observations.
11	994	5.0	269	231	500	1.16	Marked arteriosclerosis. For six months dyspnea, slight edema. Heart not much enlarged. Slight improvement. Died shortly after leaving hospital.
4	935	5.0	231	213	444	1.09	Moderate alcohol. Brassworker, ten days' history of edema. Not uremic. Heart enlarged. Arteries palpable. Relieved.
2	640	5.1	224	205	429	1.09	Tonsillitis two months ago. Edema which has increased past two weeks. Improved. Died nine months after leaving hospital.
11	1,487	5.0	216	204	420	1.06	For six months increasing dyspnea, weakness with edema. Heart enlarged and dilated. Much relieved on digitalis. Fundi show arteriosclerosis. Died two months after leaving hospital.
6	1,398	5.8	294	278	572	1.06	For three years increasing dyspnea, dizziness, weakness. Heart not enlarged. Arteriosclerosis. Relieved.
3	1,035	5.1	472	450	922	1.05	Alcoholic. Edema and ascites for three weeks. Slightly enlarged heart. Much relieved.
7	440	5.7	222	226	448	0.98	Three months increasing edema with occasional uremic attack, convulsions. Heart not enlarged. Died with a terminal pneumonia one week after observations.
7	1,643	4.9	385	395	780	0.98	Alcoholic. Dyspnea on exertion, nocturia. Much enlarged heart. Arteriosclerosis. Some improvement before discharge.
5	992	5.2	371	384	755	0.97	History of nephritis four years ago. For three months mild uremia. Blurred vision but fundi normal. Heart not enlarged. Improved. A year later in good condition.
3	890	5.3	340	352	692	0.97	Three years ago acute nephritis, at the time mild uremia, well until one month ago; slight edema and mild uremia. Slight hypertrophy of heart. Improved.
2	405	5.4	264	270	534	0.97	Mastoid operation three years ago. Albumin in urine two years ago. Since then mild uremic symptoms. Negative physical.
5	335	5.4	188	198	386	0.95	Eight years ago for three months severe tonsillitis. Past four months increasing edema and pallor. Physical negative. Died some months later.
2	868	6.0	260	280	540	0.93	Etiology obscure. Purpura for ten days. No other symptoms. Improved.
28	953	5.2	207	224	431	0.92	Discharging ear for twenty one years. Is a painter. Lead colic at 21. For eleven months increasing weakness, dyspnea and edema. Enlarged heart. Marked arteriosclerosis. Died two weeks after observations.
5	1,091	5.9	166	201	367	0.83	Nephritis (?) at 13. Headache for one year, much worse past three weeks. Heart not enlarged. Artery walls just palpable. Fundi normal.

TABLE 2—DATA OF AUTHORS' CASES ASSEMBLED IN—

Case No	Sex	Age	Clinical Diagnosis	Systolic Blood Pressure, mm Hg	Urine			
					Phenol sulphone-phthalein % in 24 Hrs	Sp Gr	Albumin	Microscopical
36	M	41	Cardiorenal disease	210	28	1 020	V S T	Few hyaline and granular casts
37	M	55	Chronic nephritis, arteriosclerosis	230	20	1 016	V S T	Rare hyaline cast W B C R B C
38	F	30	Chronic glomerulo	115	65	1 018	L T	Very few granular casts Squamous cells
39	M	28	Acute nephritis	140	30	1 025	L T	Many hyaline and granular casts Many R B C W B O
40	F	45	Cardiorenal disease, albuminuric retinitis	230	38	1 020	V S T	Rare granular and hyaline casts W B C
41	M	30	Chronic glomerulo, albuminuric retinitis	200	49	1 015	T	Many hyaline and granular casts W B C
42	M	50	Sclerosis of kidney, arteriosclerosis	240	10	1 014	S T	Few granular casts W B C
43	M	46	Chronic interstitial	260	20	1 015	V S T	Few hyaline and granular casts
44	M	46	Arteriosclerosis, myocardial weakness	150	41	1 012	V S T	Rare granular cast
45	M	19	Chronic nephritis	110	19	1 030	L T	Many hyaline, granular, fatty and epithelial casts W B O
46	F	43	Chronic nephritis, albuminuric retinitis	210	33	1 022	L T	Many granular casts W B O
47	M	20	Subacute nephritis	160	70	1 010	S T	No casts were found
48	M	56	Chronic nephritis	210		1 016	T	Few granular casts W B O
49	M	43	Chronic glomerulo	230	30	1 020	T	Numerous hyaline and granular, occasional epithelial casts W B C
50	M	25	Acute glomerulo	130		1 025	L T	Many hyaline, granular and epithelial casts R B C W B C
51	F	50	Chronic interstitial	260	42	1 020	V S T	No casts seen

—ORDER OF RATIO BETWEEN ACID AND AMMONIA—(Continued)

Urine							Remarks
Num- ber of Observ- ations	Amount c.c in 24 Hours	Acid Factors					
		Hydro- gen Ion Concen- tration	Acid N/10 c c	Am- monia N/10 c c	Acid + Am- monia	Acid - Am- monia	
9	1,300	4.9	408	497	905	0.82	Painter Chronic lead poisoning For two or three years, increasing dyspnea, precordial distress and edema Enlarged heart Arteriosclerosis Little improvement Died year later.
11	1,613	5.3	325	406	731	0.80	A year's dyspnea and edema which have been increasing Very much enlarged heart Marked arteriosclerosis Fundi show arteriosclerosis Some improvement Died nine months later
7	1,088	5.7	292	378	670	0.77	Albumin in urine since birth of child twelve years ago without symptoms Came to hospital for arthritis Heart and arteries not remarkable A year later feeling well No uremic symptoms
3	916	5.3	455	596	1,051	0.76	Sore throat for three days with development of peritonsillar abscess Acute nephritis with this Heart and arteries negative Improved
5	1,353	5.0	193	256	449	0.75	For two months fatigue, paresthesias and slight right sided hemiplegia which had nearly all disappeared at time of entrance to hospital Enlarged heart Arteriosclerosis
4	1,090	5.2	555	754	1,309	0.74	Etiology obscure Two weeks swollen face and limbs Wassermann suspicious Heart slightly enlarged Arteries not markedly sclerosed In wards was mildly uremic Slightly improved.
5	1,838	5.9	187	256	443	0.73	Six months' dyspnea, and paresthesias Two slight cerebral hemorrhages Big dilated heart Arteriosclerosis Some improvement Died six weeks after leaving hospital
7	1,936	5.5	320	442	762	0.72	Alcoholic Three months of dyspnea and palpitation Enlarged heart Arteriosclerosis Fundi show arteriosclerosis Improved Died two months later
10	1,733	6.4	176	252	428	0.70	Dyspnea, weakness and puffy eyelids for two months Enlarged heart and arteriosclerosis Improved Died a year later
26	482	5.7	215	316	531	0.68	Always well Five weeks increasing edema which was very marked at entrance Physical except for edema not remarkable Well year later
6	796	6.0	175	261	436	0.67	For past six years two or three times a year has had brief attacks of dyspnea Symptoms at entry were of cardiac decompensation and uremia Heart enlarged, arteriosclerosis Died two weeks after observation Necropsy, arteriosclerosis
6	3,433	6.4	268	397	665	0.64	No etiology No symptoms Albumin found in urine as result of examination for life insurance Physical negative
9	1,122	5.5	234	383	617	0.61	Three years' history of increasing dyspnea, headache and edema Large heart, arteriosclerosis Died in uremia and broken compensation two weeks after observations Necropsy, arteriosclerosis
3	1,090	4.9	358	586	944	0.61	Syphilis twelve years ago Positive Wassermann now For two months increasing but never severe uremia, edema Heart enlarged Arteries palpable but not tortuous Improvement Died two months later
7	640	5.2	316	548	864	0.58	Two weeks mild uremia Marked edema Always well before Physical shows nothing but edema Marked improvement
3	897	5.4	212	397	309	0.52	For two years, more or less, dyspnea Recently mild uremic symptoms Heart enlarged Arteries sclerosed Improved

excretion, unquestionably the most convenient "test" of renal function, enjoys by far the most universal popularity and use, when it shows diminished output of color it apparently serves as an approximate estimate of kidney damage. There have been reported, however, several cases of severe nephritis in which the phenolsulphonephthalein excretion was *not* markedly reduced. On the other hand, recent writers seem to agree that any marked increase of the nonprotein nitrogen in the blood is of undoubted significance and probably involves fewer failures in detecting serious disease of the kidneys than

TABLE 3—CASES IN WHICH THE FULL—

Case No	Sex	Age	Clinical Diagnosis	Sys tolic Blood Pressure, mm Hg	Urine			
					Phenol sulphone phthalein % in 2 Hrs	Sp Gr	Albumin	Microscopical
52	F	17	Chronic glomerulo	150	10	1 010	S T	Rare granular cast R B C, W B C
53	M	23	Chronic glomerulo	240		1 016	L T	Rare R B C No casts
54	M	16	Chronic glomerulo	180	15	1 020	L T	Many granular casts Many R B C, W B C
55	F	33	Chronic glomerulo, albu minuric retinitis	210		1 010	T	Very few casts R B C, W B C
56	M	42	Chronic glomerulo	230		1 008	S T	Few granular casts
57	M	29	Chronic glomerulo	130	40	1 020	S T	Hyaline and granular casts W B C
58	F	52	Cardiorenal disease, al buminuric retinitis	210	0	1 010	S T	Rare granular cast R B C, W B C

any other known test for renal sufficiency or insufficiency. Yet it may be pointed out here that there is frequently an increase in the non-protein nitrogen in conditions other than nephritis. Satisfactory determinations of noncoagulable nitrogen requires not only much more than the average clinical laboratory equipment, but considerable skill in chemical technic. This fact makes the test less applicable to general clinical use. Still less information of diagnostic and prognostic importance seems to be available in the study of sodium chlorid, lactose, potassium iodid, and water excretion.

Given a disease which extensively damages the kidney, it is reasonable to expect that several of the many functions of the kidney may

be injured in varying degrees. As the final regulation of the alkalinity of the body, which we now know varies within extraordinarily narrow limits, falls on the kidney, and as a condition of acidosis has been shown to exist in the severe grades of renal disease, it is but natural and logical to investigate the various factors of acid excretion in this connection. The data in the tables represent such an investigation.

Among the factors of acid excretion the ammonia, in certain types of nephritis, appears to be most affected. In comparing the normal with the pathological data we have found it convenient to compute the

—TWENTY-FOUR-HOUR URINE WAS NOT OBTAINED

Urine			Remarks
Num ber of Obs er vations	Hydro gen Ion Concen tration	Acid + Am monia	
9	5.3	3.00	Three months ago tonsillitis. One month ago noma. Past three weeks increasing weakness, uremia and slight edema. Heart not enlarged. Died one week after observations were made.
4	5.1	2.36	Etiology obscure. Well until two days before entering the hospital. Rapidly increasing uremia of sudden onset, coma and convulsions. Slightly enlarged heart. Fundi show edema. Died one week after observations. Necropsy, chronic glomerulo nephritis.
4	5.1	2.28	Etiology obscure. Three months' weakness and gradually increasing edema. While in wards developed pneumonia, had convulsions, died in uremia two weeks after observation. Fundi never showed changes.
5	5.2	2.14	Delivered of child three weeks ago after sudden onset of convulsions, nausea and vomiting. Increasing uremia since. Heart not much enlarged. Fundi show albuminuric retinitis. Died two weeks after observations. Necropsy, chronic glomerulo nephritis.
3	5.1	1.26	Scarlet fever at 10. Peritonsillar abscess four years ago. For a year and a half tired and weak, for a year frequently losing weight. Eyesight failing. Enlarged heart. Palpable arteries. Not improved. Left against advice.
5	5.4	1.23	Pneumonia one year before entrance, albumin in urine ever since. For eight weeks edema of legs, headaches, poor appetite. Heart not enlarged. Fundi normal. Improved.
6	5.1	1.18	Loss of weight, color and strength for months. Mild uremic symptoms for eight weeks, has been increasing. Heart enlarged. No marked arteriosclerosis. Became more and more uremic. Left against advice unimproved.

ratio between acid and ammonia, hence the column in the tables, acid — ammonia. The marked diminution in the relative as well as absolute amounts of ammonia in certain types of nephritis make it desirable to separate the cases into two groups, one with a high acid-ammonia ratio, the other with a lower or nearly normal ratio. In the former group we have included all cases above the ratio 1.40, the cases below this figure constitute the second group (Tables 2, 3 and 4). Although this separation is not quite a sharply defined one, there are relatively few intermediate cases. The number of observations on the respective cases is so variable that it has seemed best to record the means of the several observations on individual cases and to aver-

TABLE 4—GENERAL AVERAGES

	Blood Pressure	Phenol sulphonic phthalen	Sp Gr	Number of Cases	Amount of Urine	Hydrogen Ion Concentration	Acid Ammonia	Acid + Ammonia	Acid — Ammonia
I	Average of means	19	1 014	18	1,651	5 28	290	439	1 95
	Minimum mean ¹	Trace	1 010		900	5 90	144	219	1 44
	Maximum mean ¹	63	1 020		3,710	4 90	463	785	3 95
II	Average of means	33	1 019	33	1,194	5 40	280	630	0 80
	Minimum mean ¹	Trace	1 010		335	6 40	166	252	0 52
	Maximum mean ¹	70	1 030		2,321	4 90	472	1,309	1 24
Normal average ²				16	1,231	5 94	278	649	0 75

¹ These values are selected from the general table so that acid + ammonia, and acid — ammonia appear incorrect in the table ammonia values are individual low records from different cases

² Henderson, Lawrence J , and Palmer, Walter W The Several Factors of Acid Excretion, Jour Biol Chem , 1914, xvii, 305

TABLE 5—TOTAL NITROGEN IN URINE AND NONCOAGULABLE NITROGEN IN BLOOD WITH RATIOS

Case No	Volume c c	Hydrogen Ion Concentration	Acid N/10 c c	Ammonia N/10 c c	Acid + Ammonia	Acid + Ammonia	Ammonia N	Total N	Ammonia Nitrogen Ratio	Blood Nitrogen Mg per 100 c c Blood
4	1,840	5.7	294	80	374	3.68	0.112	8.8	1.3	132
	1,700	5.7	300	135	435	2.22	0.191	8.1	2.4	80
5	1,710	5.0	240	100	340	2.40	0.14	7.4	1.9	194
	2,250	5.0	308	100	408	3.08	0.14	10.0	1.4	
6	950	5.0	180	70	250	2.57	0.097	7.2	1.3	190
	1,000	5.0	213	89	302	2.40	0.125	8.5	1.5	
	795	5.0	180	71	251	2.54	0.100	6.8	1.5	
	855	5.0	203	70	273	2.90	0.097	7.1	1.4	
8	1,840	5.0	390	220	610	1.77	0.31	10.5	3.0	66
	1,320	5.3	317	164	481	1.93	0.23	7.8	2.9	
	1,380	5.3	373	163	536	2.28	0.23	9.2	2.5	
	1,660	4.9	480	202	682	2.37	0.28	11.9	2.4	
18	4,120	5.0	515	575	890	1.37	0.53	18.8	2.8	236
	3,300	5.0	410	270	680	1.52	0.38	17.5	2.2	
19	1,780	5.0	400	318	718	1.26	0.45	13.7	3.3	53
	1,430	5.0	422	384	706	1.48	0.40	11.9	3.4	
	1,610	4.9	480	400	880	1.20	0.56	16.1	3.5	
	1,500	4.9	442	350	792	1.26	0.49	14.0	3.5	
	1,350	4.9	405	345	750	1.17	0.48	14.8	3.3	
	1,280	4.9	373	327	705	1.15	0.46	13.5	3.4	
	1,375	4.9	438	405	843	1.08	0.57	15.1	3.8	
	1,670	4.7	510	605	1,115	0.84	0.85	17.6	4.8	
	1,810	4.7	620	715	1,335	0.87	1.00	19.5	5.3	
	1,700	4.7	555	740	1,295	0.75	1.04	16.5	6.3	
	1,700	4.7	387	580	967	0.67	0.81	10.9	6.8	
	1,525	4.7	382	515	897	0.74	0.73	10.2	7.1	
20	2,265	5.1	400	310	710	1.29	0.43	9.9	4.3	76
	2,420	5.1	510	440	950	1.16	0.61	14.6	4.2	
	2,500	5.3	325	270	595	1.20	0.38	11.1	3.4	
	2,100	5.3	360	300	660	1.20	0.42	11.0	3.8	
41	1,250	5.3	540	810	1,350	0.67	1.13	13.5	8.4	83
	1,320	5.2	640	684	1,324	0.94	0.96	11.8	8.1	
	1,040	5.1	535	520	1,055	1.03	0.73	11.8	6.2	
	1,840	5.0	510	1,000	1,510	0.51	1.40	10.5	13.0	
43	2,075	5.2	405	470	875	0.86	0.66	12.2	5.4	88
	1,900	5.6	304	570	874	0.53	0.80	12.7	6.3	
	2,310	5.5	348	435	783	0.80	0.61	13.0	4.7	
	2,000	5.3	330	480	810	0.69	0.67	11.0	6.1	
	1,820	5.7	334	425	759	0.79	0.60	9.0	6.6	
	1,800	5.4	270	405	675	0.67	0.57	9.0	6.4	
47	2,600	6.0	230	400	630	0.58	0.56	11.6	4.8	53
	3,700	6.7	220	320	540	0.69	0.45	6.2	7.3	
	4,100	7.0	82	400	482	0.17	0.56	6.5	8.6	
	2,800	6.9	140	250	390	0.56	0.35	4.1	8.5	
	4,000	6.1	440	510	950	0.86	0.71	12.2	5.8	
	3,600	5.8	500	500	1,000	1.00	0.70	13.8	5.1	
51	1,450	5.2	306	193	799	0.62	0.69	9.7	7.1	60
	800	5.6	155	342	497	0.45	0.48	5.6	8.6	
	440	5.3	176	357	533	0.49	0.50	6.1	8.2	

TABLE 6—DATA CONCERNING NECROPSY CASES

Case No	Aged — Ammonia	Clinical Diagnosis	Anatomical Diagnosis	Description of Kidneys*
53	2 36	Chronic glomerulonephritis, chronic endocarditis of the mitral valve, hypertrophy and dilatation of heart	Chronic glomerulonephritis, fibrous endocarditis of the mitral valve, hypertrophy and dilatation of heart, soft spleen, obsolete tuberculous of the mesenteric lymph nodes	Combined weight 236 gm Capsule adherent in places The surfaces generally finely granular and mottled with discrete and confluent pin head sized yellowish to grayish areas On section the cortical markings are obscured and the cortical substance shows discrete and confluent yellow to grayish ill defined areas and mottlings Over considerable areas the cortical substance is of a homogeneous opaque yellowish color The cortex of each kidney is about 4 mm wide Microscopical Considerable diffuse fibroid atrophy of the renal tissue Atrophy of the glomeruli Some glomeruli show proliferation of their endothelium as well as proliferation of the capsular epithelium Arteriosclerosis is not marked
55	2 14	Chronic glomerulonephritis, albuminuric retinitis, uremia	Chronic glomerulonephritis, slight arteriosclerosis, hypertrophy and dilatation of heart, anasarca, edema of the limbs	Weight of right, 156 gm Capsule strips, leaving a smooth surface mottled with brownish red areas The tissue is of good consistence, the pyramids are distinct from the cortex which measures 5 mm The ends of the blood vessels are quite distinct Weight of left kidney 92 gm The capsule strips leaving a granular red surface On section the tissue is rather tough, the markings are indistinct and the cortex measures 2.4 mm The section surfaces show pale, dull, red pyramids and the cortices mottling with pale dull grayish and brownish areas Microscopical Marked degenerative changes in the tubules with considerable increase in the interstitial connective tissue The glomeruli show well marked proliferation of the endothelium of their capillaries and occlusion of the latter by proliferated cells Marked arteriosclerosis
9	1 93	Chronic glomerulonephritis, hypertrophy and dilatation of heart, chronic passive congestion, serofibrinous pericarditis, bronchopneumonia lower left lung, edema of the lungs, moderate arteriosclerosis	Arteriosclerotic nephritis, hypertrophy and dilatation of heart, chronic passive congestion, acute serofibrinous pericarditis, bronchopneumonia lower left lung, edema of the lungs, moderate arteriosclerosis	Combined weight 254 gm Capsules removable, leaving a very granular surface of a generally red color with fine gray mottling Here and there a yellowish area about a pinhead in size is present On section the cortices are 2.4 mm inside The cut surface is generally gray, red mottled and the markings obscure or absent The renal arteries are large and the walls much thickened Microscopical Marked fibroid atrophic changes The arteries, particularly the smaller ones, show marked sclerosis There is some hyaline thrombosis The glomeruli show some proliferation and fusion of their epithelium, but the appearances are not typical of chronic glomerulonephritis

13	1 72	Chronic glomerulonephritis, albuminuric retinitis, uremia	Chronic diffuse nephropathy, hypertrophy of left ventricle, edema of the lungs, edema of stomach and intestines, chronic hypertrophic gastritis, cerebral hemorrhage, fatty degeneration of heart	<p>Combined weight 190 gm Both kidneys of the same size and general appearance Each kidney contains a number of cysts varying in size from 3 to 0.5 cm in diameter The capsule is firmly attached but it strips off clean The surface of the kidney is pale, roughly granular, due to small elevations averaging 2 mm in diameter On section the markings are obliterated Both cortex and pyramids are atrophied, the average thickness of the cortex being 2 mm The renal arteries show marked thickening and opacity of the intima Microscopical Sections of kidney show a high degree of arteriosclerosis affecting all the vessels, relatively the smallest vessels affected more than the large The glomeruli show a high degree of atrophic and hyaline change, varying degrees of this hyaline change can be seen, in the slightest it shows as a thickening of the walls of the capillary loop, this is universally present From this there is every change up to complete obstruction There is very marked connective tissue increase with atrophy of the tubules There seem to be comparatively few places in which all evidences of tubules have disappeared There is great desquamation of the epithelium chiefly from the greatly dilated tubules in the cortex It is difficult to account for this desquamation, because in many places the epithelial cells, though desquamated, show stainable nuclei In the pelvis many of the collecting tubules are filled with masses of such desquamated cells Hyaline casts are numerous</p> <p>Right 70 gm Left 135 gm The capsule of the right kidney strips with difficulty Here and there are rough puckered surfaces Cortex measures 5.6 mm On section the tissue is reddish brown and of slightly increased consistence The markings are retained The left kidney is similar to the right, only less scarred Cortex 6.7 mm Microscopical Much arteriosclerosis Areas of fibroid atrophy are present The glomeruli are often enlarged and show doubtful proliferation of their endothelium</p> <p>Combined weight of the kidneys, 265 gm The capsules strip leaving markedly granular, dark, gray, red surfaces which show a few small smooth walled cysts Section shows increase in the connective tissue The cortex and pyramids are made out, cortical markings obscured The section surfaces show minute grayish areas and streaks, cut end of the vessels are prominent Microscopical Arteriosclerosis with atrophy and fibrosis of the renal tissue The glomeruli do not show lesions characteristic of glomerulonephritis</p>
45	0 67	Chronic nephritis, albuminuric retinitis, chronic uremia	Arteriosclerotic nephritis, hypertrophy and dilatation of heart, arteriosclerosis, chronic passive congestion, thrombosis right iliac artery, infarct of spleen, acute and chronic colitis	
49	0 61	Chronic nephritis, hypertrophy and dilatation of heart, anasarca, uremia, terminal infection	Arteriosclerotic nephritis, hypertrophy and dilatation of heart, arteriosclerosis, chronic passive congestion, hydrothorax, anasarca and ascites, thrombi in right auricular appendage, chronic pleuritis	

* The anatomical descriptions, with the exception of Case 13, are taken from the pathological records of the hospital, and have been verified in every instance by Dr J H Wright We are indebted to Dr Henry A Christian, of the Peter Bent Brigham Hospital, for the autopsy findings in Case 13

age these means for the general averages rather than to obtain the average from the entire number of observations

Group 1 includes the first eighteen cases of Table 2 and the first four of Table 3. Group 2 comprises all other cases. Because of incomplete amounts of urine in the subjects of Table 3 these values are not included in the general averages of the acid factors in Table 4. The acid-ammonia ratio in Group 1 varies between 1.44 and 3.95, averaging 1.95 as against a variation in Group 2 between 0.52 and 1.24 with an average of 0.80, which is very nearly the normal value. This very striking difference from the normal in Group 1 is not due to any increase in acid excretion, for the amount remains nearly normal, but to the diminution of ammonia excretion resulting finally in a reduction in the total acid. The hydrogen ion concentration in the two groups is 5.28 in the first and 5.40 in the second, a marked increase over the normal range of 5.94. The absence of an appreciable quantity of alkali in the form of ammonia in the ratio between acid and base in the urine helps to explain the high acidity in the first group. The cause of this increased acidity in the second group is not apparent, for the acid and ammonia values are quite normal. There is considerable difference between the two groups in the average volume of urine, 1,651 c c in the first and 1,194 c c in the second. The normal average found in our earlier investigations was 1,231 c c. In both classes of cases, however, there is much variation. The factors which influence urinary volume are so many and so difficult to control that we do not care to attach much importance to this point.

Table 5 contains the detailed data of the several cases with urinary and blood nitrogen determinations. One might expect with the low amount of ammonia found in the high-ratio cases, a low ammonia-nitrogen ratio. This actually exists, as may be seen on examination of the data. Most references to metabolism in nephritis make little mention of urinary ammonia. In his book, "Metabolism and Practical Medicine," von Noorden,¹⁰ briefly reviewing the subject, seems convinced that no difficulty exists in the excretion of ammonia salts, and calls attention to the fact that when any variation does occur it is in the nature of an increase rather than a decrease in their excretion. At one time Williams¹¹ and others considered the ammonia-nitrogen ratio of distinct value in differentiating between eclampsia and uremia, but Murlin and Bailey¹² have since pointed out its unreliability. Mar-

10 Von Noorden. *Metabolism and Practical Medicine*, English Translation, Chicago, 1907, ii, 434.

11 Williams. *Pernicious Vomiting of Pregnancy*, Bull. Johns Hopkins Hosp., 1906, xvii, 71. Bibliography.

12 Murlin and Bailey. *Protein Metabolism in Late Pregnancy and the Puerperium*, Jour. Am. Med. Assn., 1912, lix, 1522.

ischler¹³ is the only investigator we have found who has made the observation that in chronic parenchymatous nephritis "in the stage of kidney insufficiency the excretion of ammonia is low, with improvement of the general condition of the disease, the daily amount of ammonia increases" In severe cases with a urinary nitrogen varying between 10 and 15 grams he found the ammonia-nitrogen ratio within the range of 0.5 and 2.8 per cent The range of this ratio in normal metabolism as given by Folin¹⁴ is 8.3 to 5.1 per cent when the urine nitrogen is 14.8 to 18.2 grams, and 4.2 to 11.7 per cent if the urine nitrogen is reduced to 4.8 to 8.0 grams

In the first group this value is strikingly low, especially as the amounts of nitrogen in the urine are low, a condition accompanying the higher ammonia-nitrogen ratios in normal individuals In Cases 4, 5 and 6 these ratios with a single exception are less than 2.0, although the urinary nitrogen does not exceed 10.0 grams and indeed is seldom more than 8.0 grams With the diminution of the acid-ammonia ratio the ammonia-nitrogen figure increases until in Cases 43, 47 and 51 both ratios may be considered normal Further evidence of marked disturbance in the kidney's function in eliminating the nitrogenous waste products is the high noncoagulable blood nitrogen in the high ratio cases The acid-ammonia ratio and blood nitrogen could not be expected to vary exactly together, but in the tables there is a general tendency for the noncoagulable nitrogen to be lower as the acid-ammonia ratio approaches normal limits Case 6 is interesting in that starting from a moderately high ratio, on a high protein diet, the urinary ammonia increased in relative amount This case was one which was diagnosed clinically as acute nephritis, and might well represent one of the milder grades of renal damage It is quite possible that the function of the kidney in respect to nitrogen elimination was improving during the course of the experiment or that the ammonia salts had reached such a high concentration in the blood that the kidney eliminated a sufficient amount to reduce the ratio between acid and ammonia The latter explanation seems more probable in view of the fact that the blood nitrogen increased rather than decreased

In the foregoing discussion of the nitrogen factors the abnormal variation has been attributed to the inability of the kidney to excrete the nitrogen constituents in a normal manner We have not sufficient data at hand to make any other supposition It is true, however, that in several cases not reported here we have found a high noncoagulable

13 Marischler, Julius Ueber den Einfluss des Chlornatriums auf die Ausscheidung der Kranken Niere, Arch f Verdauungskr, 1901, vii, 332

14 Folin, Otto Approximately Complete Analyses of Thirty "Normal" Urines, Am Jour Physiol, 1905, xiii, 45

nitrogen in the blood without any change in the acid-ammonia ratio. With this fact in mind one is tempted to speculate concerning the possibility of certain cases with high blood nitrogen in which renal insufficiency does not explain all the phenomena.

Certain relationships in the two groups between blood pressure, phenolsulphonephthalein excretion and specific gravity of the urine are not without interest. The blood pressure in the first group averages a little higher, 196 mm., than that of the second, 173 mm. The lower limit, 140 mm., was higher than in the second group, 110 mm., while the upper readings were about the same for both. The two hour phenolsulphonephthalein excretion was much lower in the first group, 19 per cent., than in the second, 33 per cent. The range in each was much the same, from a trace to 60 or 70 per cent. We would call attention to Case 10 in the first group which had a two hour phenolsulphonephthalein excretion of 63 per cent. and died in three months. Other things being equal, a lower specific gravity in the group with larger volume of urine would be expected. The average specific gravity in the first eighteen cases is 1.014, varying between the narrow limits of 1.010 and 1.020, while the range in the other cases was between 1.010 and 1.030, averaging 1.019. Albumin occurred in larger amounts in the high ratio cases. In Group 1, 5 had a large trace, 11 a trace, and 6 a slight trace of albumin, as compared with 9 a large trace, 7 a trace, 5 a slight trace, 9 a very slight trace and 1 in which it was absent in the second group.

We wish especially to call attention to the clinical diagnosis in reference to the variation of the acid-ammonia ratio. In Tables 2 and 3 with each case we have given the clinical diagnosis as it appears in the hospital records and in no case has any influence on the diagnosis been exerted by the authors of this paper. These diagnoses were made by one of the four visiting physicians to the hospital under whose charge the patient chanced to be.

The cases are collected in Table 7 with reference to the diagnoses and divided into groups as above, one with ratio greater than, a second less than, 1.40.

TABLE 7—DIAGNOSIS WITH REFERENCE TO THE ACID-AMMONIA RATIO

Group 1, acid-ammonia ratio greater than 1.40, includes Cases 1-18, 52-55		Group 2, acid-ammonia ratio less than 1.40, includes Cases 19-55, 56-58	
Chronic glomerulonephritis	15	Chronic glomerulonephritis	11
Chronic nephritis	2	Chronic nephritis	6
Acute nephritis	2	Cardiorenal disease	6
Arteriosclerotic nephritis	1	Chronic interstitial nephritis	3
Chronic interstitial nephritis	1	Arteriosclerotic nephritis	3
Syphilitic nephritis	1	Subacute glomerulonephritis	3
		Subacute nephritis	2
		Acute nephritis	2

In the group with high ratios there is a strikingly large proportion of cases supposed to be chronic glomerulonephritis, while many supposed to be some form of degenerative nephritis appear in the low-ratio group. Of the twenty-two high-ratio cases fifteen were definitely diagnosed as chronic glomerulonephritis. It is fair to add that the two cases in which the diagnosis of acute nephritis was made may have been merely acute exacerbations of a slowly progressing nephritis, while in the ones diagnosed as chronic nephritis there were some apparently borderline cases in which a definite clinical diagnosis was impossible. Syphilitic nephritis is obviously a diagnosis of convenience and may properly be considered under the head of chronic glomerulonephritis. All the cases in Group 1 were more or less uremic and must be deemed severe when one considers that eight of the twenty-two patients died in the hospital, 2 shortly and one each 3, 4, 5, 8 and 12 months, respectively, after leaving the hospital. In six cases our letter of inquiry was returned unclaimed.

In the second group the cases seem to be much more scattered among the different types of nephritis, but if the cases catalogued as "chronic nephritis," "cardiorenal disease," "chronic interstitial" and "arteriosclerotic nephritis" are taken together (as they probably deserve to be) exactly one half of the group is included. This grouping seems justifiable because the degenerative type of nephritis in most instances is indicated. Only a few of the cases in this group were diagnosed as chronic glomerulonephritis, and not one of the acute or subacute cases, either clinically or by the various functional tests employed, showed marked renal insufficiency. On the other hand, several among the cases of degenerative nephritis were uremic, and a few died in typical uremia. Our attempts to ascertain the present condition of the subjects in this group were less successful than in the preceding group. Thirteen letters were returned unclaimed. Five died in the hospital and one soon after leaving. One died in 6 weeks, 3 in two months, 2 in nine months and 3 a year after leaving. Eight of the cases are now known to be living and without symptoms.

Of the six cases coming to necropsy four had high and two low ratios (Table 5). The clinical diagnosis in all four of the high ratio cases was chronic glomerulonephritis, which in two was confirmed at autopsy. Of the other two, however, the anatomical diagnosis was, in one, arteriosclerotic and in the other chronic diffuse nephritis with a probable arteriosclerotic background. One of the cases, Case 9, was a man 61 years old whose kidneys showed on section considerable arteriosclerosis and some changes in the glomeruli which are considered in the autopsy report "not typical of chronic glomerulonephritis." The second high ratio case in which the clinical and anatomical diagnosis

disagreed was Case 13, a young man of 29 years. His kidneys on section revealed in addition to considerable arteriosclerosis, "glomeruli showing a high degree of atrophy and hyaline change" (See protocols). The two low-ratio cases were each diagnosed clinically as chronic nephritis and at necropsy proved to have arteriosclerotic kidneys.

From the clinical evidence and limited pathological data at hand it seems safe to say that severe injury to the glomeruli is commonly accompanied by reduced ammonia excretion. In view of the difficulty in harmonizing clinical pictures and functional findings with anatomical diagnoses, we would refrain from giving the impression that in the values of the acid and ammonia we have a means of estimating the function of the kidney which conforms closely to the pathological changes. It is our purpose merely to point out an interesting phenomenon which accompanies severe grades of nephritis, usually of the chronic glomerulo type and which seems to us the more important because it is in these cases we invariably find a condition of acidosis.⁵ It seems reasonable to suppose that the failure of ammonia to do its work in the regulation of the reaction of the body may be the cause of this condition.

CONCLUSIONS

We feel justified in drawing the conclusion that our cases of nephritis divide themselves into two groups possessing the following characteristics:

- 1 Cases in which the volume of urine is abnormally large, its acidity abnormally intense, and the total acid excretion much diminished (signs of a condition of acidosis which may be of renal origin). This diminished acid excretion is due exclusively to a never failing deficit in the urinary ammonia, for the value of A (acid) is, taking account of the intensity of acidity, precisely normal. In this group the late stages of glomerulonephritis predominate. It is usual to find high noncoagulable nitrogen, a much reduced phenolsulphonephthalein excretion, a high blood pressure, large amounts of albumin and low specific gravity of the urine.

- 2 Cases in which the mean urinary volume appears to be not far from normal, the acidity high and often very high, the total acid excretion often low, but not infrequently normal. The variation in this quantity is once more due to fluctuations in urinary ammonia. These cases suggest the idea that the cases of this group involve varying degrees of acidosis which are generally much milder than in the cases of Group 1. The degenerative type of nephritis and earlier stages of glomerulonephritis occur more frequently in this group. The noncoagulable nitrogen, though often increased, is not always strik-

ingly so Phenolsulphonephthalein excretion is moderately reduced, or it may be markedly diminished, blood pressure varies widely, the specific gravity averages higher than in the previous group and albumin occurs in smaller amounts

Group 1 appears to consist of an uncommonly sharply defined group of cases which, functionally at least, are of one type Group 2 may well consist of either one or more classes of disturbance of renal function, including perhaps mild forms of the condition represented in Group 1

STUDIES ON THE PATHOLOGICAL PHYSIOLOGY OF THE HEART

II THE DYNAMICS OF AORTIC INSUFFICIENCY *

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I PREVIOUS EXPERIMENTAL WORK

Since Corrigan,¹ in 1832, first described and gave a logical explanation of the collapsing pulse often associated with aortic incompetency, clinicians and physiologists alike have given their interpretations of the circulatory changes inaugurated by a leakage of the aortic valves. In this, as in other provinces of medicine, it is important to differentiate between demonstrated facts and convenient assumptions to explain clinical observations. It is but natural, therefore, that the subject should have been the cause of considerable experimental investigation.

In 1878, Rosenbach² punctured the aortic valves in rabbits by a glass rod introduced through the right carotid. This caused no variation of mean arterial pressure. Cohnheim³ confirmed this result but Goddard⁴ obtained a fall of mean arterial pressure. De Jager,⁵ in 1883, obtained no variation after puncturing the valve segments in dogs, but in rabbits he observed a fall. This he explained as due to the fact that a relatively greater insufficiency is produced in rabbits.

Kornfeld,⁶ in 1896, extended the experimental work by recording in addition the pressure in the left auricle. In a considerable percentage of his experiments the mean arterial pressure fell. He considered three possible causes of this fall: a backward leak, a deficient cardiac contraction, and a reflex dilatation of the blood vessels. The rise of right auricular pressure in some experiments favored, he believed, the first possibility. The back-flow during diastole, he reasoned, elevated the intraventricular pressure and so raised the left auricular pressure. Those cases in which the auricular pressure was not elevated he

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¹ From the Department of Physiology, Cornell University Medical College.

² The second of a series of experimental and clinical investigations of pathological cardiac conditions made by means of optically recording instruments.

1 Corrigan. *Edinburgh Med and Surg Jour*, 1832, *xxxvii*, 225.

2 Rosenbach. *Arch f exper Path u Pharmacol*, 1878, *ix*, 1.

3 Cohnheim. *Vorlesungen uber allgemeine Path*, *ii*, 38.

4 Goddard. *Acad Proefschrift*, Leyden, 1879.

5 De Jager. *Arch f d ges Physiol*, 1883, *xxvi*, 215.

6 Kornfeld. *Ztschr f klin Med*, 1896, *xxix*, 91, 344.

explained as due to a ventricular dilatation without increase in tension. Kornfeld also made the observation that the arterial pressure rapidly recovered from the fall and returned to its normal level, a fact conveniently attributed to a compensatory vasoconstriction

It is evident that studies of the mean arterial pressure are not adequate to give any clear conception of the dynamics, in fact these experiments necessitate as many, if not more, theoretical assumptions than do the clinical signs and symptoms

In 1908, Stewart,⁷ for the first time, endeavored to study the dynamic changes during separate cardiac cycles. This was accomplished by recording simultaneously the volume curves of the ventricles by a cardiometer and tambour and the arterial pressure changes by a Hürthle membrane manometer, the maximal and minimal readings being controlled by maximal and minimal valved manometers

On rupturing an aortic cusp by means of a valvulotome devised by MacCallum,⁸ he found that diastolic pressure fell more than systolic, while, in some instances at least, the contour of the arterial pulse changed. The amplitude became greater and descending limb dropped more rapidly, corresponding to the typical collapsing pulse clinically observed

The volume curve showed certain interesting but unexpected deviations—the rate of ventricular discharge estimated by the gradient of the downstroke was slower, the output per beat was increased only a trifle (5 c c) and the ventricular filling, occurring normally only in early diastole, continued throughout that phase. In spite of this extended period of filling, the ventricle was dilated less than is normally the case at the end of diastole, an observation that could be accounted for only by a greater tonicity

Two facts are emphasized by this investigator, (1) that relatively little blood regurgitates during aortic insufficiency, and (2) that regurgitation can account neither for the large amplitude of the pulse nor for its collapsing character. The reason that little regurgitation occurs is logically explained as follows. The flow into the ventricle in diastole is determined by the size of the opening as well as by the pressure. At the end of systole, however, the pressure in the aorta is quite low (not more than 15 mm above that at the end of diastole). Since the aortic leak is small as compared with the mitral orifice, blood flows more readily through the latter under low auricular pressure than through the narrow aortic leak under higher arterial pressure

The larger amplitude of the arterial pulse and its collapsing character cannot be due to a regurgitation, according to Stewart, for, (1) the

⁷ Stewart THE ARCHIVES INT MED, 1908, 1, 102

⁸ MacCallum Bull Johns Hopkins Hosp, 1906, LVII, 260

great drop of pressure occurs before the dicrotic notch, and hence during ventricular systole, and (2) the collapsing pulse disappears if the peripheral resistance is increased. Stewart therefore interprets the collapsing pulse and great fall of diastolic pressure as due to a reflex dilatation of blood vessels, for (1) such changes are known to accompany vasodilatation and (2) irritation of the root of the aorta caused in his experiments a similar fall of diastolic pressure.

Experiments similar to those of Stewart were reported in 1909 by Zollinger,⁹ who used rabbits, cats and dogs as experimental animals. He also found that the output per beat was practically unchanged after insufficiency, but that the diastolic distention was always increased. The systolic arterial pressure was slightly elevated or unchanged. The diastolic pressure was invariably reduced and the pulse pressure thereby increased. No typical change in contour could be recognized in the curves taken with a Hurthle torsion manometer.

In 1911, MacCallum¹⁰ restudied the dynamics of aortic insufficiency by means of a perfusion system of such a nature that the heart intact within the thorax and inclosed within a cardiometer, ejected its fluid into a set of rubber tubes emptying into a reservoir from which, in turn, the right heart was fed. In this way the peripheral resistance was entirely eliminated.

The production of an aortic insufficiency by means of a valvulotome still caused a low diastolic pressure, while the systolic pressure remained unaltered. The amplitude of the volume curve indicating the systolic discharge increased and the ventricles dilated somewhat. Whereas, normally, the measured volume outflow from the rubber tubes and that calculated from the volume curve corresponded, after insufficiency, the output calculated from the volume curves increased while the measured flow remained unaltered. MacCallum concluded from this that the excess volume must have regurgitated back into the ventricle.

The greater systolic discharge, together with the lower tension of the arterial wall, account, according to this investigator, not only for the greater systolic filling and large pulse amplitude, but also for the low position of the dicrotic notch without the assumption of a peripheral dilatation.

II CRITICAL ANALYSIS AND SIGNIFICANCE OF PREVIOUS WORK

It is necessary to consider critically to what extent it is demonstrated by previous experiments that the dynamic changes in aortic insufficiency are due either to aortic regurgitation or to peripheral vaso-

⁹ Zollinger. *Arch f exper Path u Pharmacol*, 1909, 1x1, 193

¹⁰ MacCallum. *Bull Johns Hopkins Hosp*, 1911, xxi, 197

dilatation It will no doubt be generally conceded that, if the production of a valvular lesion causes in an artificial circulation scheme in which peripheral changes are entirely eliminated changes similar to those in the body, it offers probable, though not absolute, evidence that the changes are not due to vascular dilatation To be satisfactory as probable evidence, however, the records previous to the lesion should have a normal contour as well as a correct placement and reproduction of a dicrotic notch After the lesion, the amplitude should be larger and the placement of the dicrotic notch should be lower This is the case in the experiments reported by Marey on a mechanical model of the circulation, but not so in the records reported by MacCallum If any conclusion could be drawn from a careful study of the *so-called dicrotic waves* before and after valvular lesions, as reported by the latter investigator, it would need to be that the dicrotic notch mounted higher on the descending limb during insufficiency (MacCallum, curves 2 and 5) As a matter of fact, however, owing to the use of inadequate apparatus, no oscillations resembling a dicrotic notch were recorded, but instead the inherent vibrations of the apparatus

On the other hand, however, no satisfactory proof has been offered by Stewart that a dilatation occurs The curves reproduced to show the possibility of producing a reflex vasodilatation on irritating the root of the aorta are clearly misinterpreted (Stewart, Figures 20 and 21) The fall of diastolic pressure was quite evidently due to a slowing of the heart¹¹ and not to a reflex dilatation The proof rests entirely on the necessity of explaining (a) the great fall of arterial pressure previous to the dicrotic notch, and (b) the supposed return of the pulse contour to normal after aortic compression or the administration of epinephrin To anticipate, it may be stated that the former can be explained on an entirely different dynamic basis, while the latter observation proves to be incorrect

The evidence seems to be conflicting as to whether an actual regurgitation occurs MacCallum found the amplitude of the volume curve increased Stewart and Zollinger obtained no change Stewart found that at the end of diastole the ventricle was dilated less than normally; Zollinger and MacCallum noted considerable distention

It is questionable to my mind whether this mode of experimentation is reliable or conclusive During the time interval required to produce the lesion the circulation may have been changed, and by the manipulation itself it is difficult not to disarrange the cardiometer enough to account for the changes A more fundamental objection, however,

¹¹ For a detailed discussion of the effect of the length of previous heart cycles on systolic and diastolic pressures of subsequent beats, see Wiggers, *Jour Exper Med*, 1914, xix, 12, also *The Circulation in Health and Disease*, Philadelphia, 1915, p 71

exists. The cardiometer is applied to two ventricles and records their volume changes simultaneously. Its use in the normal circulation is based on the presumption that the two ventricles functionate in a similar manner. Who shall dare to accurately analyze the composite curve obtained when one ventricle contracts as an after-loaded and the other as a loaded muscle? The results during insufficiency can at most show the changes in the volume output of the two ventricles. The fact that the amplitude fails to increase does not necessarily imply the failure of a regurgitation. It is conceivable, for instance, that a regurgitation may take place into the left ventricle, push the interventricular septum to the right and in so doing prevent the filling of the right ventricle by an amount equal to the increase regurgitation into the left ¹²

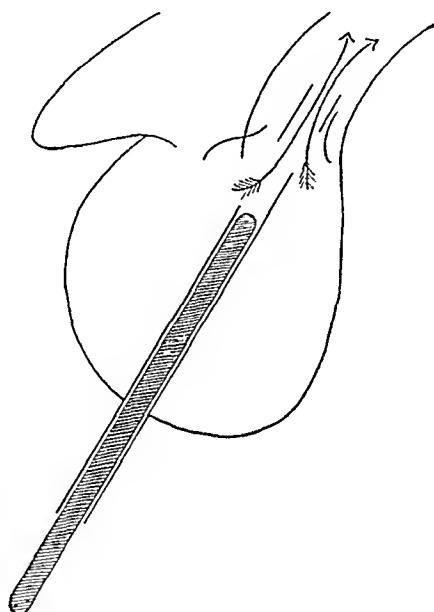


Fig 1—Diagram illustrating a simple method of producing aortic insufficiency in the expired heart

A critical consideration, therefore, leads to the conclusion that clear and convincing proof has not yet been supplied by experimental work as to the dynamic changes brought about in insufficiency.

III APPARATUS AND PROCEDURES

In this investigation the changes in the aortic and intraventricular pressures immediately after the production of valvular insufficiency were studied. The manometers, the recording apparatus and technic of their operation were essentially as described in a previous paper of this series ¹³. Mean pressure was read in addition from time to time by

¹² Cf results of Henderson and Prince, *Heart*, 1914, v, 217

¹³ *THE ARCHIVES INT MED*, 1915, *xx*, 77

temporarily opening a side tube of the optical manometers connected with a damped mercury manometer

The dogs were under chloretone anesthesia. The chest was opened after proper artificial respiration had been instituted. The pericardium was left intact as far as possible. Provisions for maintaining an effective auricular pressure, when desired, were at hand, as described in a previous paper.

Valvular insufficiency was produced in a temporary fashion on a principle similar to that previously reported in conjunction with Du Bois¹⁴. The apparatus and method are diagrammatically illustrated in Figure 1. A metal sound 10 cm long and of 5 mm bore, closed by a snugly fitting glass plunger is forced through the pericardium and ventricular musculature at the apex and entered into the mouth of the aorta so that the slot (2 cm long, 2 mm wide) on one end, palpated through the aorta, lies exactly at the level of the valves. When the plunger is withdrawn an insufficiency results. When it is pushed in, the valves close normally about the sound. The advantages of producing temporary valvular lesions in this manner over tearing or cutting the valves are (1) the lesion can be produced while tracings are taken and the apparatus remains undisturbed, (2) the degree of insufficiency can be controlled and gaged by the size of the opening, (3) normal controls as to whether the circulation has changed for other causes can be obtained after the lesions have been studied, (4) the method is simpler and more certain, requiring no preliminary practice. It is used by the students in the laboratory course of clinical physiology under Dr Du Bois, who produce one lesion after the other on the same animal.

The order of experimentation has, except for special reasons, been as follows

- 1 Record of subclavian pressure curve by a calibrated optically recording manometer
- 2 A second record after opening the chest
- 3 A normal record of the subclavian pressure alone or in combination with left intraventricular pressure after the circulatory conditions which it is desired to study have been produced
- 4 A record of same after inserting the sound into the aortic orifice
- 5 Records during temporary insufficiency
- 6 Records after normal valve action has been restored

IV THE EFFECT OF AORTIC INSUFFICIENCY ON THE CONTOUR OF THE ARTERIAL PRESSURE CURVE

Eighteen experiments have been performed. A few segments of records are analyzed as representative of the dynamic changes recorded.

14 Wiggers and Du Bois. *Proc Soc Exper Biol and Med*, 1913, x, 87

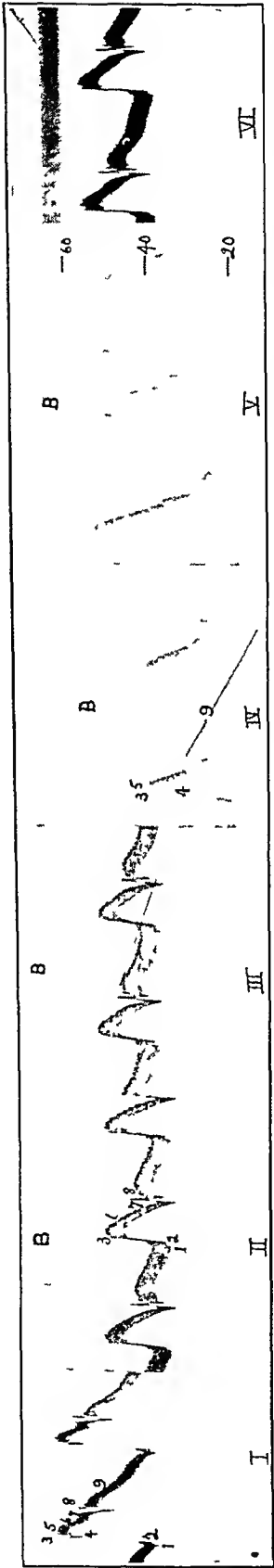


Fig 2—Six segments of records of subclavian pressure I, normal, chest closed, II, normal, chest opened, III, sound introduced, mild stenosis, IV, mild degree insufficiency, V, marked insufficiency, VI, base line (description in text), which remains unchanged

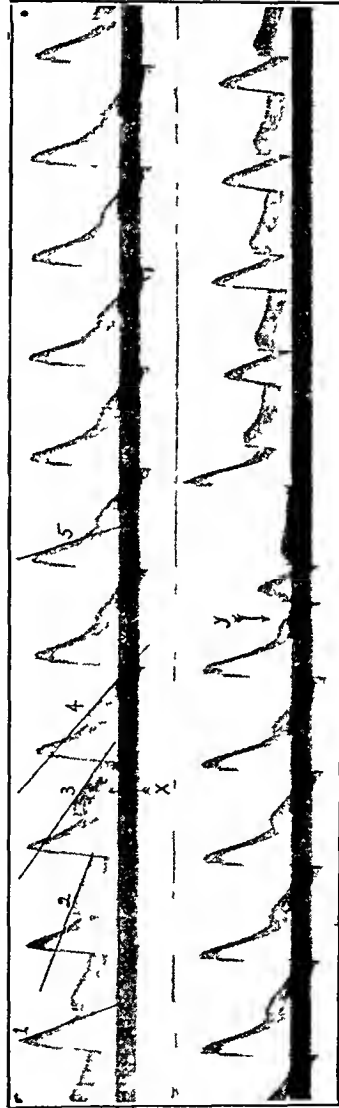


Fig 3—Continuous record of subclavian pressure during production of insufficiency at 1 and restoration of normal conditions at 2. First two beats after 2 are due to accidental extra systole and postcompensatory pulse beat after 2. The third wave after 2 shows normal again

a Arterial Curves Obtained in Cases with Impaired Systolic Output

Experiment C 59, Feb 16, 1914 (Figure 2)

I Subclavian pressure recorded by optical manometer ($N = 118$), mean pressure 74 mm mercury. The curves show all the details described by Frank, namely, 1-2, preliminary oscillations during the isometric period of systole, 2, 3, 4, preliminary oscillation of the arterial blood column, 5, systolic summit, 6, systolic decline, 7, end of systole and beginning of incisura, 8, vibration of closing valves (amplitude = 15 mm), 9, gradual decline during diastole.

II Same, immediately after opening the thorax, estimated hemorrhage, 10 cc. The systolic pressure has fallen more than the diastolic, the primary wave (2, 3, 4) has almost disappeared, the systolic fall (6) is more marked and the pressure at the end of systole is low. The incisura (7) is more gradual in its drop and the valve vibrations are slightly increased in amplitude (16 mm) but the period is unchanged.

III Same, after inserting sound. A slight stenosis has been produced in this case, as is shown (a) by the more gradual rise of the ascending limb (causing the broader band of light), (b) by the round top and entire absence of any trace of the primary oscillation.

IV Mild aortic insufficiency combined with previous slight stenosis. Heart rate exactly the same. The changes observed are: The primary oscillation (1-2) is entirely absent, the primary oscillation (3-4) returns, the systolic summit is very slightly higher (compared to base line, B), the pressure at the end of systole (7) is slightly lower, the rate of diastolic drop (9) is more rapid and the pressure at the end of diastole is much lower.

V Marked insufficiency. Same general changes as in IV but more pronounced. Systolic pressure is much higher and diastolic pressure much lower (compared to base line, B). The primary oscillations (2-3, 4) are larger.

VI Normal curve taken immediately after sound was withdrawn from the valve opening. In comparing this curve with II it is evident that the condition of the heart and circulation has improved rather than suffered as a result of manipulation. Both systolic and diastolic pressures are higher than in II, while the curve approximates more nearly that obtained from the unopened chest.

The experiment was repeated in still another way. While the record was being taken, as shown in Figure 3, an insufficiency was suddenly produced. This occurred early in diastole, as shown by the arrow. Immediately, the slope of the diastolic portion became steeper. In the first beat after insufficiency the systolic summit is slightly lower, in the second beat the primary oscillation is indicated, the upstroke becomes steeper (narrower line) and the systolic summit mounts to its normal level.

Comments. It is apparent that the mere act of opening the thorax at once alters the pressure relations in the aorta. The fact that the systolic pressure decreases more than the diastolic, as shown in the second segment of Figure 2, indicates that the change is due to a diminished output in consequence, probably, of the decreased effective pressure in the left auricle. *It may be pointed out that the effects of valve lesions have probably been studied only under these abnormal conditions by those investigators who applied cardiometers to the heart.* Such experiments, though carried on during a hypodynamic state are not without interest, however, as they are presumably typical of a certain class of clinical cases in which an insufficiency associated with a mild stenosis supervenes when the effective venous pressure is unusually low. Paradoxical as the statement may sound, it is evident that from a dynamic point of view an insufficiency is

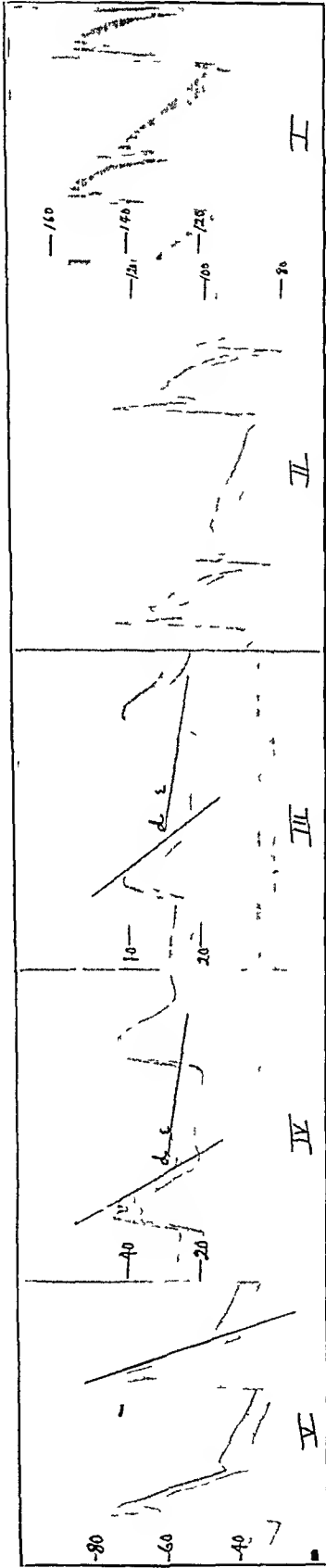


Fig 4—Five segments of records of subclavian pressure. *I*, normal, chest closed, *II*, normal, chest open, *III*, same during poor action of heart, *IV*, marked insufficiency, *V*, insufficiency during epinephrin

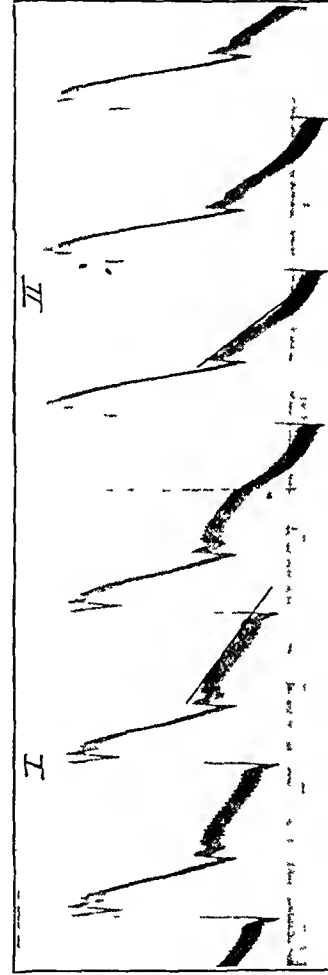


Fig 5—Two segments of records of subclavian pressure showing effect of aortic insufficiency when peripheral vessels were previously dilated

apparently beneficial in such instances. The curves of the central arteries, which were rounded and devoid of secondary oscillations, such as are indicative of an efficient circulation, regain many of their normal features, such as the primary oscillation, the larger amplitude and sharp incisura (IV and I in Fig 2). As far as the slope of the descending limb is concerned, the pressure falls more rapidly during systole, making the pressure reached at the end of systole somewhat lower, but the greatest fall occurs during the diastolic portion, and this accounts for the very low pressure at the end of diastole.

b The Arterial Curves Obtained When the Muscular Power Is Impaired

Experiment C 62, February, 1914. Figure 4 (curves mounted in order from right to left). Subclavian pressure curve with very sensitive manometer ($N = 50$). The lower frequency probably accounts for the large primary oscillation and valve vibrations.

I Chest closed, mean pressure 144 mm. Curve shows all the normal details and additional vibrations of the sensitive undamped instrument.

II Chest open—mean pressure 78 mm.

III After marked artificial respiration (apnoea?) when the heart had become weaker and the output small—mean pressure 25 mm. The arterial curves lose all their normal characteristics.

IV Aortic insufficiency of marked degree. The amplitude of the pressure change becomes greater, the systolic pressure is higher and evidence of a primary oscillation reappears. The diastolic pressure is slightly lower, the gradient of the slope is more rapid both in systole and diastole. The normal curve taken after this resembles the curve shown in III.

V Epinephrin during insufficiency. Both systolic and diastolic pressures rise, but the pressure curve is still of the collapsing type. Mean pressure 50 mm. The primary oscillation becomes more prominent, giving the top a bifurcated appearance (pulsus bisferiens). *During systole the pressure falls more steeply in spite of intense vasoconstriction.* This leads one to infer that the rate of systolic fall is not governed by peripheral constriction or relaxation, but by the height of pressure at the beginning of systole.

Comments. When, in addition to a low venous pressure, the inherent response of the ventricular muscle is poor, aortic insufficiency does not cause variations of great amplitude. Both systolic and diastolic pressures are low. Neither a distinct incisura nor valvular after-vibrations occur. The systolic summit shows a distinct notch. As far as the changes in the descending limb are concerned the fall during systole is more rapid, but the diastolic slope remains unaltered. This is the case whenever the pressure during entire diastole is very low. Epinephrin intensifies the collapsing nature of the pulse.

c The Arterial Curves Obtained When the Venous Supply and Functional Power Are Normal but the Peripheral Resistance Is Low

Experiment C 60, Feb 18, 1914. Figure 5. Dog under chloroform anesthesia, slow saline infusion.

I The curve is taken with the chest open. Venous pressure equals 50 mm in the left auricle. Nitroglycerin previously administered. The curve shows all the details of a normal pulse except that the incisura is not so sharp, the amplitude is large and the pressure falls rapidly during systole.

II Curve during insufficiency All the details of the low resistance pulse are retained with the exception of the preliminary oscillations (1, 2, 3) occurring during the isometric period The oscillations are all increased in amplitude, the systolic summit rises higher and the diastolic pressure reaches a lower level than the normal

Comments. When the peripheral vessels are dilated and the output of the heart is normal, records of the largest amplitude are obtained, for, added to the tendency of a low resistance to increase the amplitude, is the effect of the lesion The amplitude becomes greater because the systolic pressure is elevated and the diastolic pressure lowered While the gradient of the pressure fall increases somewhat during systole, the most rapid drop responsible for the low pressure at the end of diastole occurs after the incisura

d Cases with Normal Output and High Peripheral Resistance

Experiment 6 Feb 24, 1914 Figure 6 After opening the thorax the artificial respiration was reduced to a minimum, the dead space increased and a slow saline infusion continued The thoracic aorta was slightly compressed by a special clamp

I Mean pressure, 106 mm mercury Curve shows characteristics very similar to those of the curves from the unopened thorax The broad systolic summit is accounted for by the higher resistance The numbers correspond to those of Figure 2 The valvular vibrations are reduced owing to a higher pressure

II, III Two degrees of insufficiency The preliminary oscillations 1, 2, disappear, the primary vibrations (3) are larger and the top is sustained during systole (5), as in normal curves The rapid drop at the incisura occurs in a normal manner The change occurs in diastole beginning at 7 The fall is very rapid and complete so that the diastolic pressure is lower The systolic summit also falls but not in proportion.

IV After administration of epinephrin, 1 cc of a 1:50,000 solution The entire curve has a larger amplitude The ejection is more rapid but the contour of the systolic portion remains unaltered. The diastolic drop is more rapid, on the other hand, and of greater magnitude, indicating a greater regurgitation

Comments: This type of experiment is comparable to clinical cases of insufficiency in which good heart action is associated with some peripheral sclerosis increasing the total arterial resistance In such cases the change in contour is almost entirely limited to the diastolic portion Increasing the activity of the heart, as by the injection of epinephrin, does not modify the contour of the systolic portion but increases the amplitude of the entire curve

e The Effect of Aortic Insufficiency on the Contour of the Intraventricular Pressure Curves

Experiment 62 Feb 25, 1914 Figure 7 Simultaneous tracings of subclavian and left intraventricular pressures The relative position of points is shown at the start of the second and third records

I Normal peripheral resistance, low venous pressure and a systolic output less than normal Mean pressure, 40 mm The intraventricular pressure curve possesses the smooth character common to curves in which the initial intra-

ventricular tension is low (see previous paper) The isometric rise (A) merges almost imperceptibly into the ejection period (B) C represents the active relaxation, and D the interval of diastasis

II Aortic insufficiency with changes typical of the arterial pulse in this condition—mean pressure 24 mm The cycles are equal to those of I An isometric period (A) persists but is shortened The end of the ejection period is difficult to determine Important, however, is the fact that the ejection period plus the relaxation period ($B + C$) remains unaltered, while the period of diastasis (D) is longer

III Aortic insufficiency after injection of saline and 2 c.c. of a 1:100,000 solution of epinephrin The intraventricular record was shifted in relation to the base line in order to record the full amplitude The most important change is that the intraventricular curve no longer remains smooth A distinct bend in the ascending limb (2) separates the isometric and ejection periods The systolic summit (3) rises exceedingly high

IV Normal curves during the action of epinephrin The initial tension (1) is reduced but not in corresponding measure as the subclavian pressure is raised The period of the isometric rise (A) is longer and terminates at a higher level (2) The summit (3) is lower, the period of active relaxation (C) is unchanged, but diastasis (D) is shortened in cases in which the same heart cycle is retained

Comments In regard to the intraventricular pressure curves, as compared with the arterial curves, aortic insufficiency causes, not an abolition, but merely a shortening of the isometric phase The maximum pressure, as in normal hearts, is determined largely by the initial pressure which, during insufficiency, may be greater This constitutes the immediate reserve mechanism of the heart which causes directly after the production of a lesion, a more vigorous output In consequence of this continued greater activity, the ventricle probably hypertrophies According to these conceptions, hypertrophy is a sequel, not a cause of an unusually large output of the heart in aortic insufficiency The effect of insufficiency on the duration of diastasis, as revealed in these records, is precisely the opposite of the results of Stewart Whereas this investigator observed a shortening or abolition of the period of diastasis, these curves show a distinct lengthening Neither does it appear that the rate of active relaxation has altered The evidence that the tonus changes was entirely lacking in all experiments

V SUMMARY AND DISCUSSION

The tracings obtained in this investigation, of which the illustrations are but selected segments, indicate that the details of the curves in aortic insufficiency depend, to a considerable degree, on the condition of the heart and the peripheral vessels at the time that the lesions are produced Since all of these combinations and others are probably found in clinical cases, it may be well to summarize the chief changes in tabular form

TABLE OF CHANGES IN AORTIC INSUFFICIENCY

Conditions of Circulation	Systolic Summit	Systolic Portion of Fall (to Onset of Incisura)	Diastolic Portion of Fall (After Valve Vibration)	Lowest Diastolic Pressure
Low venous pressure, decreased systolic output Inherent action of heart good	Higher, more peaked	Gradient, somewhat steeper	Gradient, markedly steeper	Greatly depressed
Inherent power of heart poor	Slightly higher, bifurcated peak	Gradient, steeper	Rate of fall unaltered	Unaltered
Systolic output normal, peripheral vessels dilated	Higher, increased amplitude of primary notch	Unaltered	Gradient, steeper	Greatly depressed
Systolic output normal Peripheral resistance somewhat increased	Slightly decreased	Unaltered	Gradient, much steeper	Greatly depressed

While the details of the curves vary under different conditions of the circulation, they show, in addition, certain constant changes, the significance of which can be definitely stated in dynamic terms. These changes it is desirable to discuss more at length.

1 During diastole, the pressure invariably falls more rapidly¹⁵. Indeed, this is the chief fall accounting for the low diastolic pressure. The contrary records obtained by a Hurthle membrane manometer from animals and by clinical sphygmographs from man, must be attributed to faulty apparatus which exaggerates the systolic portion by fling and cannot record the events which distinguish diastole from systole.

Since the change in diastolic slope occurs within the interval of a single heart cycle and is independent of dilatation of vessels by nitroglycerin and constriction by epinephrin, it is evidently associated with the effect of the lesion itself. It is, however, quite unnecessary to assume that a large quantity of fluid regurgitates. It is essentially the *pressure back-flow* that it is important to recognize.

Quite contrary to expectation, the intraventricular pressure curve during diastole shows no deviation in its contour. The curve merely

¹⁵ The only exception occurs when the diastolic pressure is very low, owing to a very small output.

fails to return to its normal level and in diastasis undergoes no further elevation, though arterial pressure continues to fall. The regurgitation of pressure occurs early after relaxation. The initial tension, that is, the tension to which the ventricle is submitted at the onset of the next ventricular contraction, is therefore never elevated so as to even approximate the intra-arterial diastolic. No detailed explanation can be offered without further investigation.

2 The preliminary oscillations normally present during the isometric period fail to occur. This is most readily explained by assuming that the ejection begins immediately after the onset of ventricular contraction. This would accord with the *current view* of the dynamics of this lesion. It is commonly recognized that the normal heart contracts as an *after-loaded muscle*, i. e., as a muscle which raises a weight so supported that it exerts its force only during the period of action. In other terms, the ventricle normally requires an isometric interval during which the pressure is raised sufficiently to open the semilunar valves and cause its ejection of blood. During aortic insufficiency, on the other hand, it is generally supposed that the ventricle is exposed to the full load of the aortic pressure during diastole and therefore contracts as a muscle from which a weight is permanently suspended. It has no isometric period, but the blood is ejected at once.

A careful comparison of the aortic and intraventricular records indicates that this view is not precisely correct. The curves shown in Figure 7, for example, clearly indicate that an isometric interval exists but that it is shortened. This is accounted for by the observation already pointed out, namely, that although the initial intraventricular tension at the onset of systole is somewhat greater during insufficiency, it is always less than the diastolic pressure within the aorta. Hence a time interval is required to elevate the intraventricular pressure to the level of the aortic diastolic pressure. The relatively low diastolic pressure and the more rapid elevation of intraventricular pressure combine to make the isometric period short. The failure of preliminary oscillations may be due to the fact that the small rise of pressure which is necessary before ejection occurs is not sufficient to cause a bulging of the valve segments.

3 The pressure rises more rapidly and the primary peak is augmented or is reestablished when absent previous to the production of the lesion. In order to understand the more rapid rise of the curve and the augmentation of the primary oscillation, it is necessary to bear in mind what may be termed *the dynamic law of the ventricle*. It has been shown by Frank in the case of the frog's ventricle, by me for the right ventricle of mammals and by Straub, Starling and Piper for

the left ventricle, that the rapidity of the tension rise, the maximum height which the intraventricular pressure reaches, as well as the vigor of ejection, are determined, within limits, by the initial tension within the ventricle. It has already been pointed out that without producing any deviation in the pressure curve, the initial tension is greater in aortic insufficiency. The ejection period also begins at a lower level, owing to the lower diastolic pressure. Consequently, a larger quantity of blood is ejected into the aorta and with greater rapidity than is normally the case. It should be recalled that the primary oscillations are due (Frank) to the vibration that the entire blood column undergoes when suddenly ejected. If, for any reason, the vigor of ventricular ejection becomes small, the primary oscillation may entirely disappear.

The production of an aortic insufficiency by increasing the vigor of discharge at once acts to restore or augment the primary oscillation. The ejection may be so sharp that several vibrations occur, as in Figure 6, III and IV.

4 The more vigorous ejection of a larger quantity of blood in the earlier part of systole also raises the systolic summit to a higher level and accounts for the high systolic pressure. It is apparently not necessary to assume the existence of a cardiac hypertrophy or an arteriosclerosis in patients in order to explain this high pressure.

5 The high systolic summit once reached is not maintained, but drops away very rapidly during systole, so that, at the beginning of the incisura, the pressure is often lower than the normal. That this is not due to an increased peripheral flow brought about by vasodilatation is evident from the facts (1) that the change occurs too rapidly (within a single beat), (2) that it is present when the vessels are previously dilated by nitroglycerin and (3) that it is intensified rather than prevented by epinephrin. It is probably explainable by the fact that, while a larger quantity of blood is ejected with greater vigor early in systole, the total systolic discharge is not much increased. Consequently, during the latter portion of systole, less blood per unit time is actually ejected, and the peripheral flow exceeds the cardiac output per unit time. It is therefore more pronounced when the vessels are dilated and entirely absent when the aorta is clamped and the area of peripheral flow restricted.

CONCLUSIONS

From these considerations it may be concluded (1) that the characteristic changes of the pressure curve in the central vessels, as recorded by optical manometers, cannot be explained by any reflex vasometer mechanism set in operation by the production of an insufficiency, and (2) that the dynamic changes are accounted for by the

fact that an aortic regurgitation increases the initial intraventricular tension, owing to a regurgitation of pressure during diastole, this, in turn, causes a more vigorous ejection of a larger blood volume in the early portion of the next systole. This may be accompanied by an actual decreased ejection during the latter portion of systole, thus, at once, accounting for the facts (a) that the systolic decline becomes steeper and (b) that the total systole output may not increase appreciably beyond normal.

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AN ATTEMPT TO DETERMINE THE DIAGNOSTIC IMPORTANCE OF HEAD'S ZONES OF HYPERALGESIA *

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The following work is an attempt to estimate the practical importance of cutaneous hyperalgesia in the diagnosis of visceral disease

Ross¹ published, in 1887, an article on the segmental distribution of sensory disorders. He first took up the distribution of the sensory nerves and showed that in man it is somewhat similar to that in the primitive vertebrates except for some disarrangement caused by the development of the limbs. In the primitive vertebrate each segment of the cord supplies an area of the body surface immediately over it and the viscera under this area. In man the relation of the viscera to the body surface has so changed that the somatic segment and the viscus supplied by the same cord segment are no longer one over the other. Pain, he said, might be splanchnic or somatic, splanchnic pain being vaguely felt over the region of the diseased organ causing it, somatic pain being felt in the sensory nerves derived from the corresponding cord segment. He then gave briefly the distribution of the somatic pain for each viscus and named the dorsal segments through which the stimuli from the splanchnic nerves are diffused to the somatic nerves.

The following tabular outline gives the segmental supply of each organ, the location of the referred pain, and the other symptoms associated through the same nerve supply, according to Ross

Stomach Dorsal 4, 5, 6—pain between the shoulders and in front of the chest, oppression or constriction in the left side (spasm of intercostals) brow-ache (pneumogastric)

Lungs Cranial, 10 dorsal (?)—pain at midsternum and between the shoulders, palpitation, gastric disorders, rumbling of the bowels

Pleura Cervical 4 (phrenic)—pain over outer tip of clavicle, otherwise directly over seat of disease

Heart Dorsal 2 diffusing to dorsal 1, 3, 4 and cervical 8—pain in left chest and between the shoulder blades and down inside of left arm

Liver Dorsal 7, 8—pain at angle of scapula

Bowels Dorsal 10, 11—pain in the back and in front about the umbilicus

Kidneys Somatic and splanchnic pain coincide

* Submitted for publication March 3, 1915

¹ Ross, James. On the Segmental Distribution of Sensory Disorders, Brain, 1888, x, 333

Pelvis and Ureter Lumbar 1, 2—pain down inside of thigh along ileo-inguinal and genitocrural and external cutaneous nerves

Testicle Lumbar 1—dragging pain in loin, ileoinguinal nerve

Ovary Lumbar 1, 2, 3—pain above iliac crests posteriorly (posterior branches of second lumbar), above the groins (ileoinguinal), and in iliac region and the hip-joints

Bladder Sacral 3—pain along urethra to tip of penis (pudic nerve)

Rectum Sacral 3—pain in urethra (pudic) and down back of thigh (small sciatic)

Uterus Sacral 2, 3, 4—pain over lower sacrum Os uteri Sacral 3—coccygeal neuralgia

Mackenzie² published his first work on sensory symptoms in visceral disease in 1892. He noted the site of the pain in diseases of the various organs and found that frequently it did not correspond with the situation of the viscus involved but was approximately constant in location for a given organ, and was often accompanied by tenderness of the spines of certain vertebrae and by hyperalgesia of the skin over the site of the pain. He made no attempt to connect the viscera with definite spinal segments but mapped out roughly the skin areas involved in the pain. The following tabular outline shows the site of the referred pain in diseases of the various organs according to Mackenzie

Heart Pain over midsternum from right of midline to beyond the left nipple line or under the left breast, down the left arm, between the shoulder blades, occasional hyperalgesia (Note agreement with Ross)

Lungs No referred pain, pain when present due to accompanying pleurisy which is localized to site of disease (Compare Ross)

Esophagus Pain over lower sternum

Stomach Pain in upper epigastrium, tenderness in epigastrium and to left over sixth, seventh and eighth interspaces (Note disagreement with Ross)

Small intestine Pain on either side of umbilicus (In agreement with Ross)

Large intestine Pain midway between umbilicus and symphysis

Rectum Pain over upper sacrum (In disagreement with Ross)

Uterus Pain over upper sacrum (In agreement with Ross)

Uterine contraction Pain in midline above symphysis

Liver No pain (Compare Ross)

Gall passages Pain in midline or a little to right at level of lower epigastric and upper umbilical areas Hyperalgesia frequent

Kidney No pain (In disagreement with Ross)

Pelvis and ureter Pain from above middle of iliac crest in lumbar region downward and inward to region of penis or scrotum (In disagreement with Ross)

Bladder Pain along urethra or under surface of penis to tip of penis

It will be seen by comparing the two outlines that Mackenzie and Ross disagree frequently as to the site of the referred pain

Mackenzie concluded that the pain of visceral organs was entirely an associated pain due to stimulation of the spinal centers of sensory nerves

² Mackenzie, James Sensory Symptoms Associated with Visceral Disease, *Med Chron*, 1892, xvi, 293

Head, following the work suggested by Ross, gave the first results of his work³ on the disturbances of sensation in visceral disease in 1893. He recognized definite areas of hyperalgesia in connection with symptoms or signs of irritation of certain viscera and found in addition certain maxima in those areas where the hyperalgesia was greatest and which might be present alone. Following the idea that herpes zoster was inflammation of the posterior roots,⁴ he carefully worked out the areas of distribution of a large number of cases of this disease and

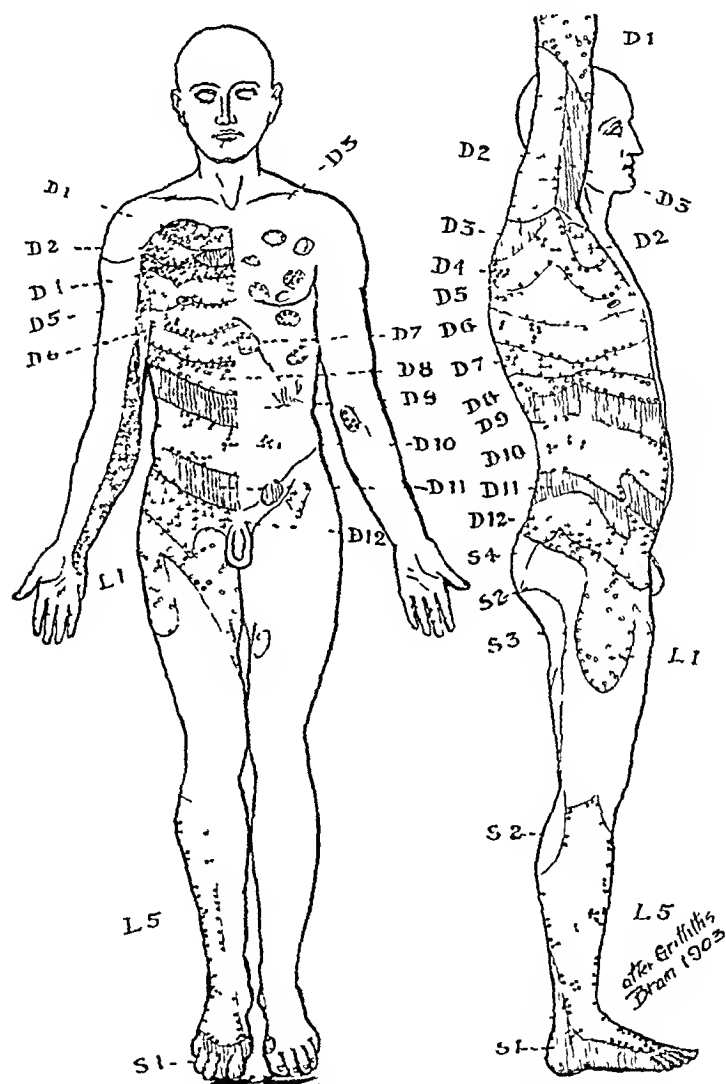


Fig 1—Head's zones of hyperalgesia

found that they agreed with the hyperalgesic areas mapped out in visceral disease, in that they did not overlap, had the same distribution, and the same maxima. Thus he was able to argue that his hyperalgesic areas represented a disturbance set up in different cord segments by afferent visceral impulses. Beginning at the second rib he found thir-

3 Head, Henry. On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease, Brain, 1893, xvi, 1.

4 Von Bärensprung. Ann d Charité, Krankenhaus zu Berlin, 1861, ix, 2, p 40. 1862, x, 1, p 37, 1863, xi, 2, p 96.

teen areas which fitted into one another. The upper borders of certain ones he was able to identify as belonging to certain spinal segments by comparison with the upper border of analgesia in a few organic lesions. The first area beginning at the second rib was found to represent the first dorsal segment. The sequence was then uninterrupted down to the first lumbar segment inclusive. The second, third and fourth lumbar segments were found not to be affected in visceral disease and to form a "gap." The fifth lumbar and four sacral segments were represented by five additional areas. A similar

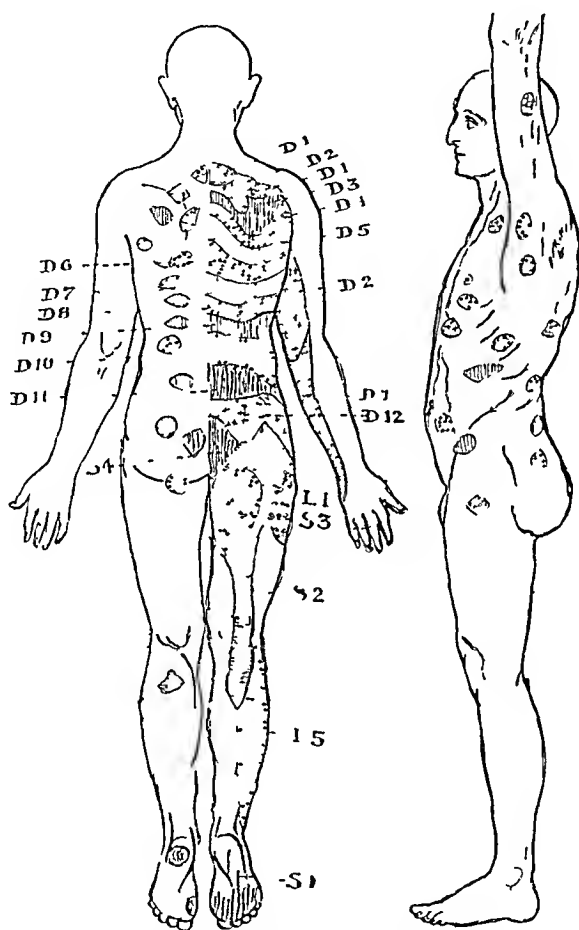


Fig 2—Head's zones of hyperalgesia

"gap" was formed by the fifth, sixth, seventh and eighth cervical segments. The distribution of the cutaneous pain fibers from those segments not affected in visceral disease was determined by organic lesions of the cord and by herpetic eruptions. Thus the whole of the body and limbs was mapped out into areas, each of which represented the cutaneous distribution of the pain fibers given off from one segment of the cord (Figs 1 and 2).

The following classification taken from Head's article shows the segments receiving fibers from the different viscera

- Heart Dorsal 1, 2, 3—cervical plexus (depressor?)
 Lungs Dorsal 1, 2, 3, 4, 5—cervical plexus (vagus?)
 Stomach Dorsal 6, 7, 8, 9—cardiac end, 6, 7, pyloric end, 9
 Intestines (A) down to upper part of rectum, dorsal 9, 10, 11, 12 (B)
 rectum, sacral 2, 3, 4
 Liver and Gallbladder Dorsal 7, 8, 9, 10 (6?)
 Kidney and Ureter Dorsal 10, 11, 12 The nearer the lesion lies to the
 kidney the more is the pain and tenderness associated with the dorsal 10 The
 lower the lesion in the ureter the more does the lumbar 1 tend to appear
 Bladder (A) Mucous membrane and neck sacral (1)—2, 3, 4
 (B) Overdistention and ineffectual contraction, dorsal 11, 12,
 lumbar 1
 Prostate Dorsal 10, 11—(12), lumbar 1—sacral 1, 2 and 3
 Epididymis Dorsal 11, 12, lumbar 1
 Testis Dorsal 10
 Ovary Dorsal 10
 Appendages Dorsal 11, 12, lumbar 1
 Uterus (A) In contraction, dorsal 10, 11, 12, lumbar 1
 (B) Os uteri, sacral (1), 2, 3, 4, (lumbar 5)

Head found that there was a tendency for the pain and tenderness caused by visceral disease to spread to other areas and that this spread followed general laws. Frequently they became bilateral or involved areas, having no connection with the affected organs. Certain areas were more easily affected in this manner than others, as the tenth dorsal or the sixth dorsal in women, and the seventh dorsal in men. Anemia, fever or mental trouble, were found to be frequent causes for generalization in which at times the maxima of many areas were affected. Some cases of hysteria of the cerebrospinal type had areas of analgesia with borders corresponding to those of the segmental areas.

He regarded the reference of pain in visceral disease as of the same nature as allochiria. The viscera having a lesser degree of sensibility than the surface of the body and being in close central connection with it, the afferent pain stimuli are accepted by a psychical error as coming from the area into which they are diffused. Though insisting so strongly on the reference of pain to the body surface, he believed that visceral pain was also referred to the organs affected, being there of a dull, aching character instead of a sharp, stabbing character.

Hyperalgesia of the skin in disease of the underlying viscera he explained by the exaggeration of the afferent sensory skin stimuli in the cord segment which had been disturbed by the abnormal visceral stimuli. He never found hyperesthesia as a result of visceral disease and concluded that the central paths of the pain fibers from the skin and viscera were closely connected.

In 1893, Mackenzie's⁵ second paper emphasized several points on which his work was found to conflict with that of Head. After the appearance of Head's first work, Mackenzie again carefully observed a number of cases in which he found hyperalgesia in visceral disease and a number of cases of herpes zoster, but found that he could not make the areas agree with those of Head.

In a second paper⁶ Head took up the subject of referred pain in the head and neck. As no attempt was made in the present investigation to determine areas of hyperalgesia above the trunk, this portion will be very briefly discussed. He attempted to show that such organs as the nose, the eye, the ear, the teeth, the tongue, the salivary and other glands, the tonsil, the larynx and the brain, stood in relation with cutaneous areas of the head and neck to which pain was referred in diseases of these organs. Herpetic eruptions over the head and neck were found to occur over these same areas. He found that headaches accompanying disease of the thoracic or abdominal viscera were accompanied by hyperalgesia of head areas, and that the latter were always located with reference to the dorsal or other area involved. Thus the situation of a headache in cardiac disease was determined by the dorsal segment affected. He carefully worked out the distribution of the pain fibers in the branches of the fifth cranial nerve, and showed that they did not correspond with his areas.

In a third paper⁷ he took up diseases of the heart and lungs and showed the groups of areas affected in various pathologic conditions. Here, as before, he admitted the presence of local pain and of deep tenderness in both diseases of the heart itself, and of the pericardium, as distinguished from referred pain and superficial tenderness.

He found that with an aortic murmur, pain was liable to be referred to the second, third and fourth dorsal, and sometimes to the third and fourth cervical areas. When a systolic murmur at the apex was also present, or when it developed, pain was no longer referred. In aneurysms of the aorta, pain was referred according to the situation of the dilatation as follows: ascending aorta, to the third and fourth cervical, first, second, third and occasionally fourth dorsal, usually of the left, but also of the right side, arch of aorta to the inferior laryngeal area of both sides, descending aorta to the sixth, seventh and eighth dorsal areas. Simple mitral regurgitation, or cases with a mitral murmur obliterating the first sound, and with a diastolic

5 Mackenzie, James. *Some Points Bearing on the Association of Sensory Disorders and Visceral Disease, Brain*, 1893, xvi, 321.

6 Head, Henry. *On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease. Part II, Brain*, 1894, xvii, 339.

7 Head, Henry. *On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease. Part III, Brain*, 1896, xix, 153.

murmur, were found not to have pain. With a mitral systolic murmur, a sharp first sound at the apex, and usually a presystolic or diastolic murmur, pain was referred to the fifth, sixth, seventh, eighth and occasionally to the ninth, dorsal areas. In distention of the liver produced by right-heart failure, pain was referred to the eighth, ninth and tenth dorsal areas. In paroxysmal cardiac pain, or angina pectoris, the referred pain was widespread and involved practically all the cardiac segments.

He found the most important considerations for the production of referred pain to be "firstly the maintenance of considerable tension within a cavity of the heart, accompanied by, secondly, a sudden accession of tension (owing to regurgitation) at the moment when the walls of the cavity are dilating after systole." Thus, in aortic stenosis the tension in the ventricle is high, and if there be a coincident regurgitation at the aortic valve, then during diastole there is a rush of blood back into the ventricle at a comparatively high tension and the conditions for referred pain are present. Similar reasoning applies to mitral stenosis in its early and middle stages. From the above considerations he tabulated the sensory supply of the heart and aorta as follows:

Transverse arch of aorta	Inferior laryngeal segment
Ascending arch of aorta	Cervical 3, 4, dorsal 1, 2, 3, (4)
Ventricle	Dorsal 2, 3, 4, 5 (6?)
Auricle	Dorsal 5, 6, 7, 8 (9?)

He showed that this sensory supply agreed quite well with the embryologic development of the various chambers of the heart.

Pain in connection with disease of the lungs was found to be either local or referred. The pain of pleurisy coincided precisely with the situation of the area of pleura involved and was accompanied by deep tenderness but not by superficial hyperalgesia.

Referred pain was found most frequently in those cases of phthisis in which the progress of the disease was marked by successive bronchitic attacks in which previously healthy lung tissue was involved. This he thought was due to the fact that the end organs of the sensory nerves in the portion of the lung under invasion were still intact and capable of being irritated and conveying impressions. With the disease well advanced, the nerve endings were destroyed and that portion of the lung was no longer able to cause referred pain. He found referred pain and superficial tenderness particularly liable to "spreading," and attributed this to the cachexia and the rise in temperature by which each advance of the disease was accompanied. Very roughly he was able to estimate the portion of the lung under invasion by the cutaneous areas involved in the hyperalgesia. The innervation of the

lung was found to be as follows Lungs cervical 3, 4, dorsal 3, 4, 5, 6, 7, 8, 9

In 1900,⁸ Head published the results of a number of necropsies in cases of herpes zoster, showed that the disease was accompanied by an inflammatory process of the posterior root ganglion and in general substantiated his previously worked out areas for each spinal segment

In 1901,⁹ he followed this by work which attempted to show that psychical states in visceral disease were connected with the hyperalgesic areas on the head and neck which were found in conjunction with involvement of certain spinal segments Thus a patient with double aortic disease had widespread referred pain and tenderness over the left side of the thorax, headache and scalp tenderness over the forehead and temple, and hallucinations of sight, depression and suspicion

In 1912¹⁰ Mackenzie reviewed and elaborated the whole subject of referred pain and tenderness He believed that all visceral pain was referred and gave experimental evidence to show that the viscera were absolutely insensitive to all ordinary forms of stimulation The muscles and subperitoneal tissue, as well as the skin, he found became hyperalgesic when the corresponding cord segment became irritable from visceral disease, and muscle spasm over the diseased organ originated in the same segment Cutaneous hyperalgesia he found comparatively rare, and when present he was unable to find that the areas involved fitted those worked out by Head

Experimental work by Hertz¹¹ throws grave doubts on the referred character of all pain, at least in disease of the alimentary tract He showed that the stomach was indeed insensitive to ordinary stimuli but that sensations of pain were caused on distention of this organ This he was able to prove by inserting inflatable rubber bags into the stomach When distention was caused at a certain level of the esophagus the patient was able, fairly accurately, to locate the level of the painful stimuli, and the cutaneous surfaces over both front and back of the thorax were not found hyperalgesic Thus he concluded that pain in disease of the alimentary tract was caused by distention of the circular fibers of the muscular coat and that the sensory nerves of the sympathetic system became sensitive to this distention and

8 Head, Henry, and Campbell, A W The Pathology of Herpes Zoster and Its Bearing on Sensory Localization, Brain, 1900, xxiii, 353

9 Head, Henry Certain Mental Changes that Accompany Visceral Disease, Brain, 1901, xxiv, 345

10 Mackenzie, James Symptoms and Their Interpretation, 1912 London Shaw & Sons

11 Heitz The Sensibility of the Alimentary Canal London, 1911 Oxford University Press, pp 50-52

expressed it as pain which was referred to the place usually occupied by the viscus according to the law of average localization. Such distention is caused when forceful peristalsis meets such an obstruction as a spastic pylorus, almost separates the pyloric antrum from the remainder of the stomach by a circular wave of constriction and raises the tension of the portion beyond the advancing constricting ring.

T. C. Noeggerath and von Salle¹² in a study of early tuberculous lesions in children, found that of forty-six patients, of whom twenty-four were clinically suspected of tuberculosis, "Head's zones" could be demonstrated in sixteen, or 66 per cent. Hyperalgesia was not found in children without lung signs. The areas found involved were the fourth cervical and second, third and fourth dorsal.

The work of Head was brought to mind by a case of aneurysm of the aorta in which there was severe pain and hyperalgesia of the skin corresponding almost exactly with the diagrams of Head. It was then determined to examine a large series of ward patients for hyperalgesia in order to determine the frequency of its occurrence and estimate, if possible, its importance in diagnosis. The investigation covered a period from July 1, 1913, to July 1, 1914, during which 460 patients were examined. Hyperalgesia was found as a rule somewhat indefinite, inconstant and difficult to elicit. In no case was it so marked that the head of the pin was mistaken for the point. Doubtless errors have been made, but they were unavoidable in these patients, many of whom were of a low grade of intelligence and too ill to pay much attention to a long examination.

Laryngitis, acute. 2 cases showed no hyperalgesia.

Bronchitis, acute. 6 cases. Of these one was almost in uremic coma on admission so that the bronchitis was a postmortem finding, and in another there was a possibility of tuberculosis. Three of this group complained of pain but none showed hyperalgesia.

Chronic bronchitis. 12 cases. Pain was not a feature except in one case, and this patient had no hyperalgesia.

Infarct of lung. 3 cases; in two the infarcts were postmortem findings. The patient in Case 143 had severe pain and a localized friction rub without hyperalgesia.

Abscess of lung. 4 cases, one patient complained of pain, none showed hyperalgesia.

Bronchopneumonia, in 12 cases, was terminal or a postmortem finding in eleven. One patient, Case 264, complained of discomfort in the epigastrium but not of pain. He was a diabetic who died three

¹² Head's Zones in Early Tuberculosis of Childhood, *Jahrb f Kinderheilk*, 1911, xxiv, No. 74, reviewed by Michael, *Am Jour Dis Child*, 1912, iii, 186.

days after admission to the hospital. A small area of hyperalgesia was found (see Fig 3) corresponding approximately to one of the maxima of the eighth dorsal area. This would indicate, according to Head, disturbance in the heart, lungs, stomach, or the liver and gall passages. At necropsy he was found to have a healed chronic suppurative pleurisy of the right base, tuberculosis of the lungs healed at the base, healed pneumonia of the left lung with carnification at the base, recent pneumonia, and an acute gastro-enteritis.

In 2 cases of lobar pneumonia both patients had pain in the chest, but hyperalgesia was not found.

Of tuberculosis of lungs there were 38 cases. Head found that pain was a more frequent feature of this disease during bronchitic

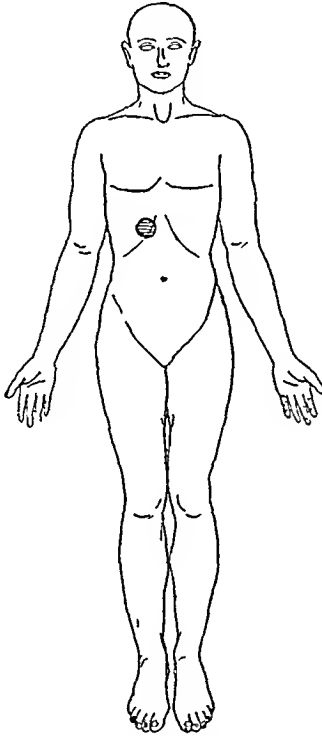


Fig 3—Conditions noted in Case 264, hyperalgesia found in broncho-pneumonia. A maximum of the eighth dorsal area was involved.

attacks which marked the spread of the disease. On account of the short period of time that these patients were allowed to remain in the hospital, the opportunity was not found to determine definitely when new involvement occurred. Furthermore, on account of the unreliability of the patient's statements as to the duration of his symptoms, it was often not possible during the short period of observation to determine whether the disease was acute or chronic. In a large majority of the cases, the disease was well advanced, frequently it was far advanced. In only 11 cases was the probable duration under two years. Seventeen patients complained of pain which seemed connected

with their lung infection. Of these only 5 were probably fairly acute cases. Of the 17 patients complaining of pain, evidence of pleurisy was found in nine, the pain was abdominal in two, precordial and accompanied by palpitation in one, and in the arms in one. Thus only three cases in this group had pain without evidence of pleurisy. Hyperalgesia was found in Case 84. This patient, aged 39, had had cough, fever, chest pain and hemoptysis for three months at 22, and cough, expectoration and some night sweats at times to date of admission. During the last five months of this period he had had pain in the back, chest, and arms, increased by movement. Examination showed evidence of a thickened pleura, some infiltration and adhesions over the lower half of the left lung, and slight changes throughout

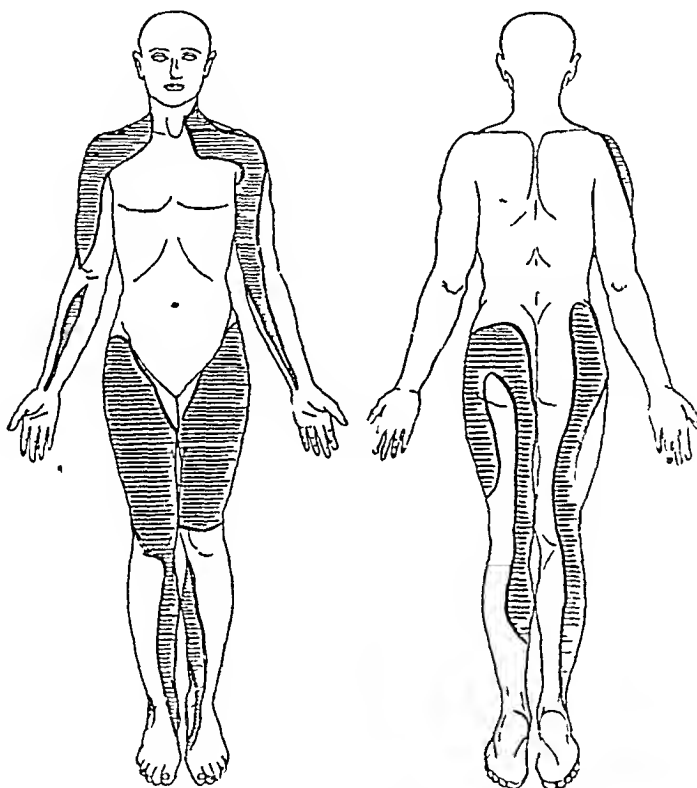


Fig 4—Conditions noted in Case 84, hyperalgesia in tuberculosis of the lungs. Portions of the first, third and twelfth dorsal, first and fifth lumbar, and first, second and third sacral areas were involved.

The sputum was occasionally blood tinged but no tubercle bacilli were found. There was hyperalgesia as shown in Figure 4, corresponding to portions of the first, third and twelfth dorsal, first and fifth lumbar and first, second and third sacral areas, but to an equally great extent to areas into which visceral pain is not referred, according to Head. Involvement of the first and third dorsal would indicate disease of the heart or lungs, of the twelfth dorsal and first lumbar, disturbance of the kidney and ureter, bladder or epididymis, none of which were found. Involvement of the first lumbar, first, second and third sacral areas would indicate disease of the prostate which was apparently

normal Disease of the vertebrae was not found It is evident that in this case the hyperalgesia cannot be accepted as an indication of visceral disturbance unless its wide extent to areas not usually affected by visceral disease be accounted for by "spreading"

Six (chronic adhesive) out of 37 cases of pleurisy were found only at necropsy, eleven were apparently healed or of long standing, eleven were acute, eight were serofibrinous and one was demonstrated tuberculosis

In chronic pleurisy, 11 cases, one patient complained of pain which seemed connected with the lesion Hyperalgesia was not found in this group

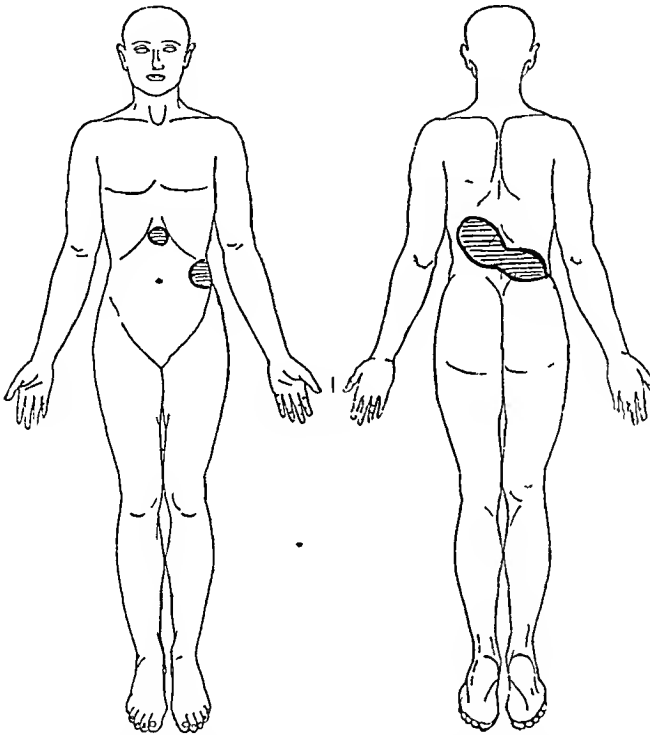


Fig 5—Conditions noted in Case 287, hyperalgesia in serofibrinous pleurisy The maxima of the seventh dorsal areas and portions of the ninth, tenth and eleventh dorsal areas were involved

In acute fibrinous pleurisy, 11 cases, the pleurisy was terminal in two, in another the lesion was small and probably due to an infarct The remaining eight patients complained of pain Hyperalgesia was not found

In serofibrinous pleurisy, 8 cases, pain was a feature in every case and was more severe and constant than in the preceding group Hyperalgesia was found in Case 287 This patient gave a history of general indisposition for a year, followed three weeks before admission by pain in the left chest and back, steadily increasing in intensity, until he felt dizzy and unable to work Examination showed signs of fluid in the left chest, the heart displaced to within 1 cm of the right nipple line,

the liver and spleen enlarged and palpable, the latter tender, and hyperalgesic, as shown in Figure 5, corresponding approximately with the maxima of the seventh dorsal area anteriorly, and portions of the ninth, tenth and eleventh dorsal areas laterally and posteriorly. The pain was apparently due to pressure on the various organs in close proximity, as the pleural surfaces were separated by about 4,000 c c of fluid. Involvement of the seventh dorsal might come either from the heart or lung, both of which were under great pressure. No explanation was found for the involvement of the other areas.

There was one case of tuberculosis of the pleura. Patient 108 had had palpitation and shortness of breath, precordial pain, cough, loss of weight, and night sweats, for five months before admission. The left

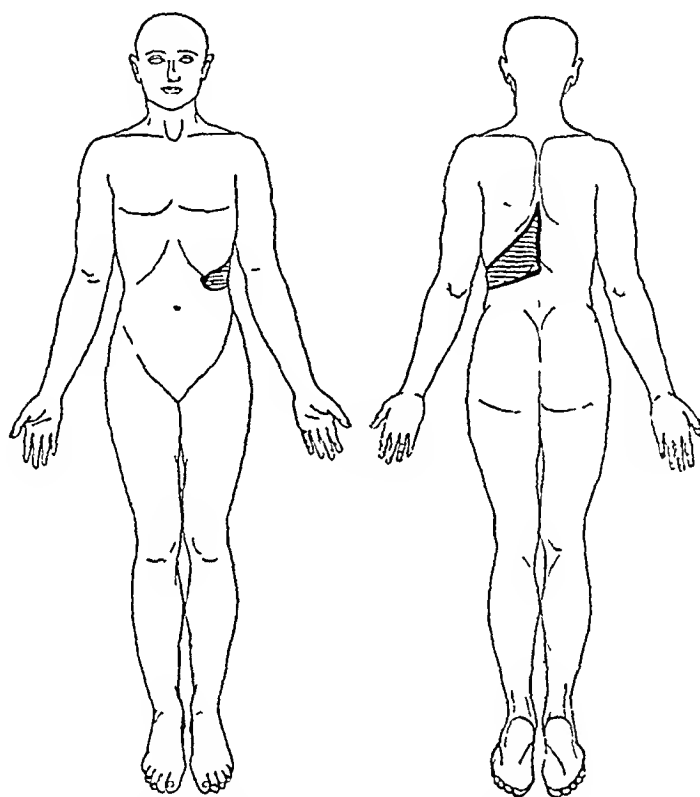


Fig 6—Conditions noted in Case 108, hyperalgesia in tuberculous pleurisy. Portions of the seventh, eighth and ninth dorsal areas were involved.

pleura contained a large amount of fluid, the heart was displaced as far as the right anterior axillary line, and the urine contained a heavy cloud of albumin, hyaline and granular casts. Tubercle bacilli were demonstrated in the pleural fluid. The Wassermann reaction was ++— in the blood. Hyperalgesia was found as shown in Figure 6, corresponding anteriorly with a portion of the ninth dorsal area, posteriorly with portions of the seventh, eighth and ninth dorsal areas. The hyperalgesia seems to follow quite definitely the course of the intercostal nerves instead of agreeing with one or more segmental areas. Here as in the previous case it seems impossible to say whether

the site of the disturbance is in the heart or the lung. Thus, in 116 cases of disease of the larynx, bronchi, lungs and pleura, 30, or 25.8 per cent, complained of pain, and of these, 4, or 13 per cent, showed hyperalgesia which seemed very doubtfully connected with the respiratory system.

Of 40 cases of valvular disease of the heart two were classed as acute endocarditis and were without pain. Six were classed as subacute endocarditis and two patients of this group complained of pain. There were thirty-two classed as chronic endocarditis or chronic valvular disease, and eleven patients of this group complained of pain which seemed connected with the heart.

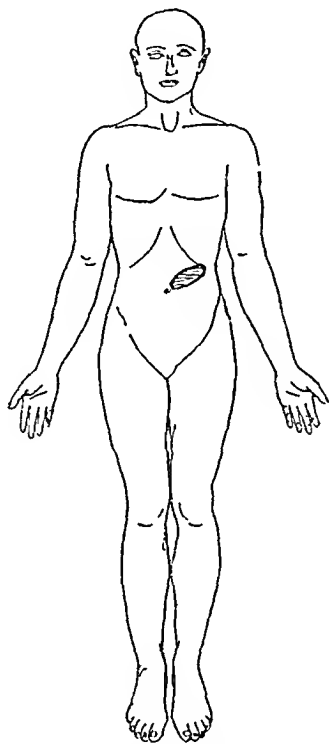


Fig. 7—Conditions noted in Case 188, hyperalgesia in mitral insufficiency. One of the maxima of the ninth dorsal area was involved.

Head found that the lesions most favorable for the production of cardiac pain were aortic regurgitation (without mitralization) and mitral stenosis in its early and middle stages. The cases have therefore been grouped according to lesions.

Aortic insufficiency 11 cases, six of these patients had pain. Hyperalgesia was found in one case but involved one leg only and was apparently due to a spondylitis.

Mitral insufficiency 17 cases, five patients in this group had pain. One, Case 188, showed hyperalgesia. This patient, aged 67, gave a history of early scarlet fever, rheumatism and sore throat. Three years before admission, he developed a chronic cough and later sore-

ness under the sternum and over the upper abdomen and occasional pain down the left arm. Examination showed a chronic bronchitis with emphysema, a moderately enlarged heart, with a mitral murmur, some edema of the lungs, an enlarged and tender liver, edema of the legs and general arteriosclerosis. There was hyperalgesia as shown in Figure 7, corresponding approximately with one of the maxima of the ninth dorsal area. Here, as in other cases, it is impossible to say whether the disturbance in this segment was due to distention of one of the chambers of the heart, slight infection of the lungs or to enlargement of the liver.

Mitral stenosis 10 cases; two patients in this group complained of pain, and one had hyperalgesia. This patient, Case 227, a man of 27,

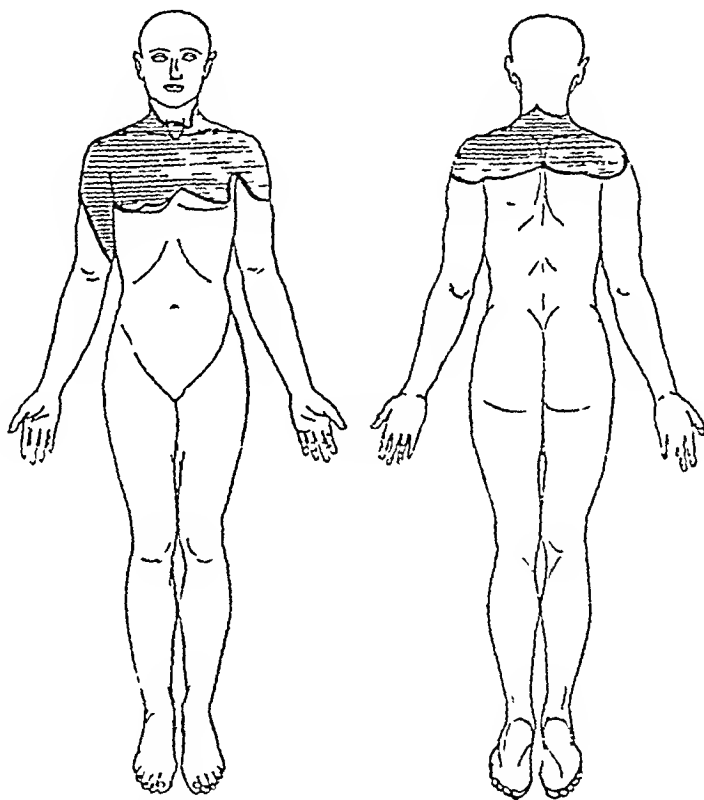


Fig 8—Conditions noted in Case 227, hyperalgesia in mitral stenosis. The inferior laryngeal, sternomastoid, sternonuchal, and first, second and third dorsal areas were involved.

had a history of previous sore throat, and joint infections following and possibly due to gonorrhea. He had had precordial pain, dyspnea and palpitation, and finally, several years before admission, stiffness of most of his joints, including his spine, with pain on movement. Examination showed pyorrhea, a mitral lesion with slight stenosis, slight hyperthyroidism, a palpable spleen, periarticular thickening about many of the joints, particularly of the ankles and knees, and extreme rigidity and considerable kyphosis of the dorsal and cervical spine. There was hyperalgesia as shown in Figure 8, involving the inferior laryngeal, sternomastoid, sternonuchal, and first, second and

third dorsal areas This hyperalgesia corresponded to the area over which pain was felt on motion of the spine This fact, with the evident spondylitis, makes it seem possible that the hyperalgesia was due not alone to the cardiac condition but to the superposition of afferent cardiac pain impulses on centers already made irritable by the spondylitis

Syphilis of aorta and aortic valves 7 cases, three of these patients had pain, hyperalgesia was not found

Arteriosclerosis of aorta and aortic valves 3 cases, one patient in this group had pain, hyperalgesia was not found

Arteriosclerosis of coronary arteries 1 case (demonstrated at post-mortem), this patient had attacks of stabbing precordial pain without hyperalgesia

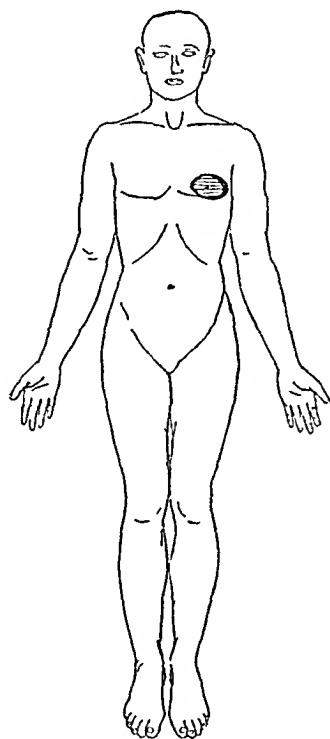


Fig 9—Conditions noted in Case 139, hyperalgesia found in a case of angina pectoris The maxima of the fourth, fifth and sixth dorsal areas were involved

Angina pectoris 2 cases, one, Case 139, showed hyperalgesia This patient gave a history of attacks of knife-like pain over the heart dating back eight years and accompanied for two years by a feeling of constriction about the chest, a sense of impending death, choking, and an irregular pulse Examination showed an enlarged heart, auricular and ventricular extrasystoles and cutaneous hyperalgesia as shown in Figure 9, corresponding to the maxima of the fourth, fifth and sixth dorsal areas, all of which may be affected in diseases of the heart

Aneurysm of aorta 2 cases, both these patients had pain while only one had hyperalgesia. This patient, Case 206, had a history of cough, expectoration, pain in the chest, and headache for four months. Examination showed a large aneurysm of the arch of the aorta which apparently was not in contact with the chest wall or the bodies of the vertebrae and hyperalgesia as shown in Figure 10, corresponding to the maxima of the seventh, eighth and ninth dorsal and the sternomastoid area. The dorsal hyperalgesia had no connection with the aneurysm and remained unexplained.

Myocarditis 25 cases, in this group were placed those patients having signs and symptoms of myocardial insufficiency without evi-

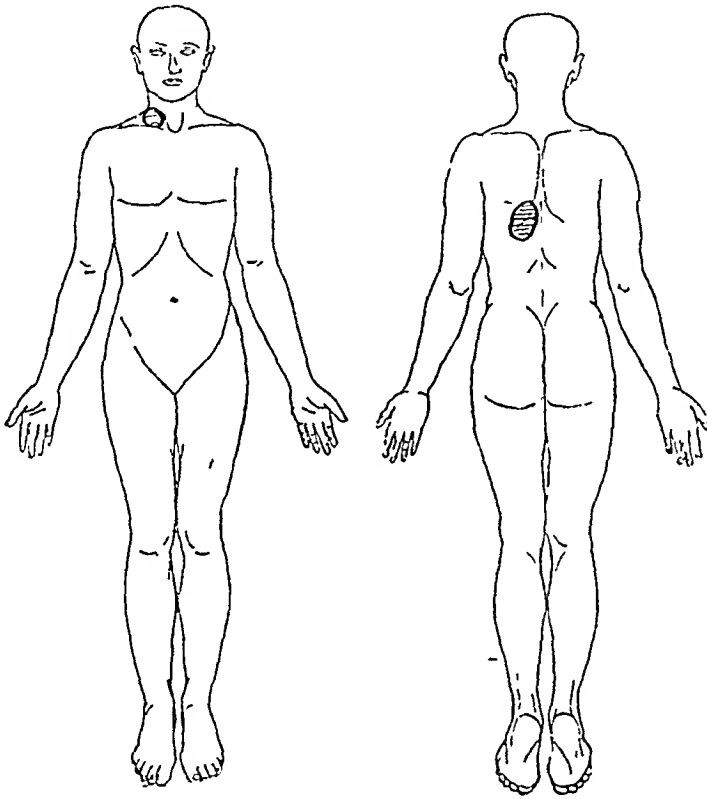


Fig 10—Conditions noted in Case 206, hyperalgesia found in a case of aneurysm of the aorta. The maxima of the seventh, eighth and ninth dorsal and the sternomastoid areas were involved.

dence of a valvular lesion. Nine patients complained of pain which in four cases was in the epigastrium and probably due to enlargement of the liver. Hyperalgesia was not found.

Chronic pericarditis 3 cases, one was not found till necropsy. Two others both had pain and hyperalgesia. Patient in case 352 gave a history of slight pain in the chest at times for two years. Ten days before admission this increased so that it hurt him to breathe and was accompanied by fever, malaise, weakness, and loss of weight. Examination showed slightly cyanotic lips, a low pitched friction sound at the apex in mid diastole, a temperature of 101, a pulse of 100, and

30 respirations to the minute While in the hospital he developed very severe pain and oppression in the chest Hyperalgesia was found as shown in Figure 11, corresponding to the maxima of the fourth dorsal area, which according to Head would suggest the ascending arch of the aorta, the ventricle, or the lungs All of these viscera were normal so far as could be determined Head found that the pain in inflammation of the pericardium was purely local and accompanied by deep tenderness, a view with which the facts of the case just described do not agree Patient 24 had had an illness about nine months before characterized by shortness of breath, chills and fever After that he found himself unable to work without pain in his chest There was

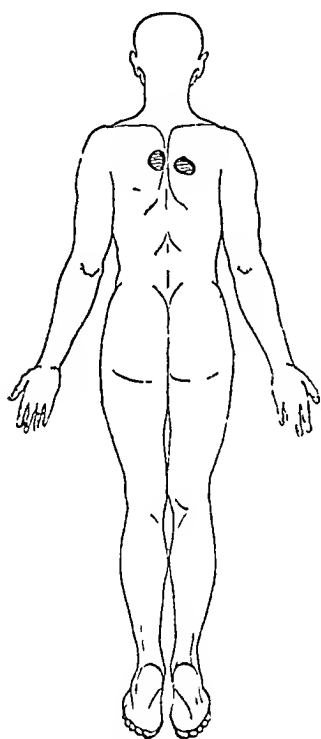


Figure 11

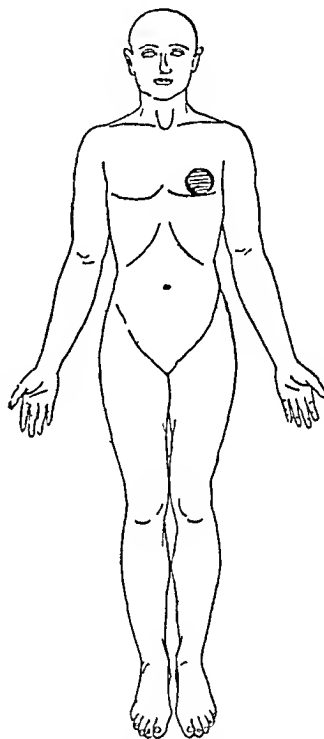


Figure 12

Fig 11—Conditions noted in Case 352, hyperalgesia in a case of pericarditis, The maxima of the fourth dorsal areas were involved

Fig 12—Conditions found in Case 24, hyperalgesia found in a case of adhesive pericarditis The maxima of the fourth, fifth and sixth dorsal areas were involved

a clicking sound at the apex heard late in systole and hyperalgesia as shown in Figure 12, corresponding to the maxima of the fourth, fifth and sixth dorsal areas

Adherent pericardium 2 cases These patients had neither pain nor hyperalgesia

Thus in 83 cases of disease of the heart, pericardium and aorta, 33, or 39 per cent, had pain, and 6, or 7 per cent, had hyperalgesia Of those complaining of pain, 18 per cent showed hyperalgesia The

inferior laryngeal, sternomastoid, sternonuchal and first, second, third, fourth, fifth, sixth, seventh, eighth, and ninth dorsal areas were found affected

Carcinoma of esophagus 3 cases, two of these patients had pain without hyperalgesia, the third complained only of discomfort in the epigastrium but had hyperalgesia. This patient, Case 60, gave a history, dating back six months, of discomfort in the epigastrium, followed by progressive difficulty in swallowing, loss of weight, and strength. Examination showed signs of an old right-side apical tuberculosis, an esophageal obstruction at the level of the heart, an enlarged liver and hyperalgesia as shown in Figure 13, corresponding to portions of the eighth and ninth dorsal areas. The patient later died and

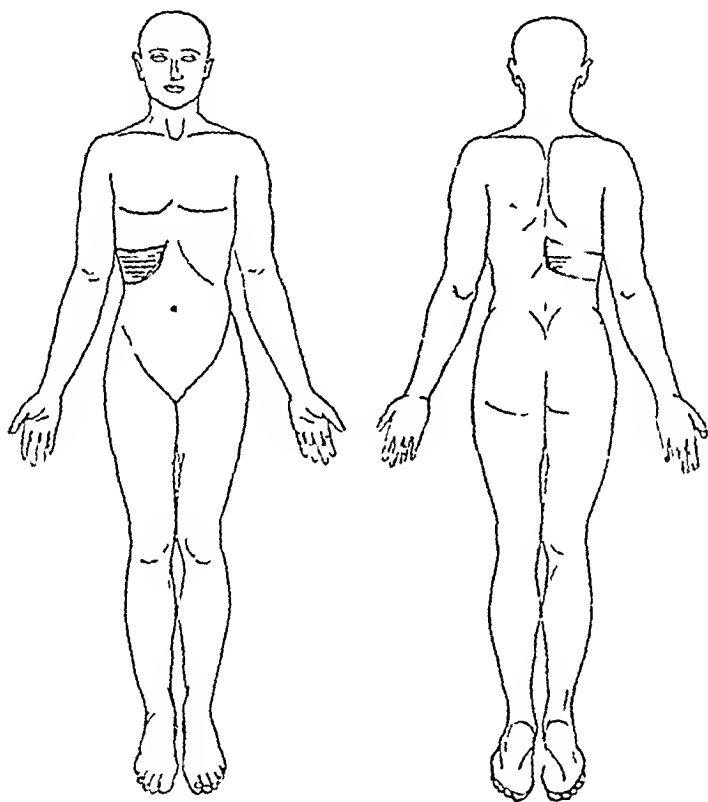


Fig 13—Conditions found in Case 60, hyperalgesia in a case of carcinoma of the esophagus. Portions of the eighth and ninth dorsal areas were involved

necropsy showed healed tuberculosis on the right, carcinoma of the esophagus and gangrene of the left lung. In a case given by Head, the fifth, sixth, seventh and eighth dorsal areas were affected on both sides

Hyperchlorhydria 1 case, showed no pain or hyperalgesia

Hypochlorhydria 4 cases, showed no pain or hyperalgesia

Ulcer of stomach 9 cases, in each of these pain was a prominent feature. Hyperalgesia was found in three. Case 100 gave a history of attacks of sharp pain in the epigastrium and left back coming on about half an hour after meals relieved by vomiting and accompanied

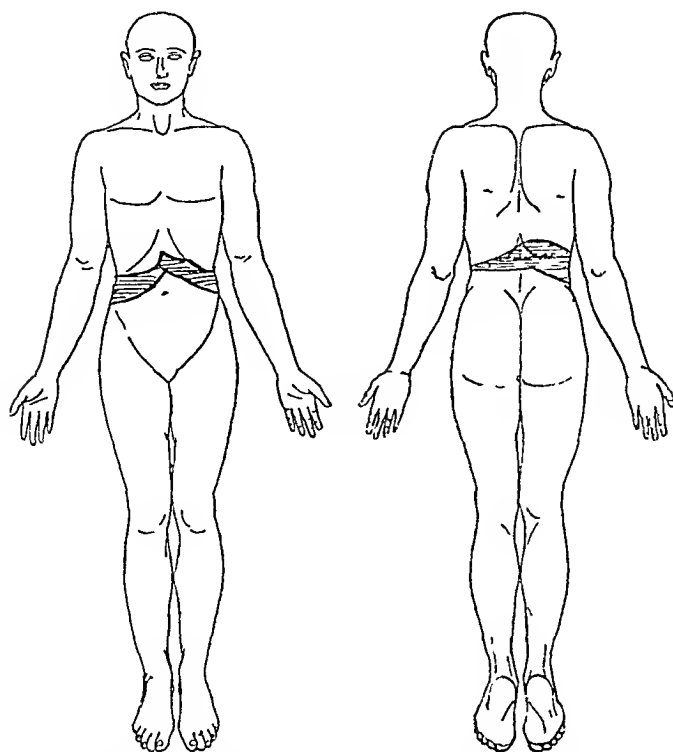


Fig 14—Conditions noted in Case 100, hyperalgesia found in a case of ulcer of the stomach Portions of the eighth, ninth and tenth dorsal areas were involved

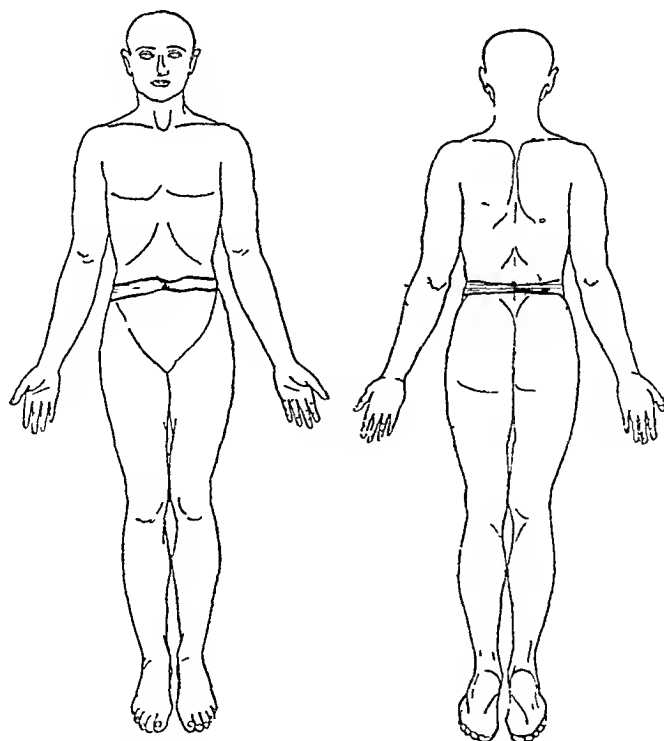


Fig 15—Conditions noted in Case 282, hyperalgesia found in a case of ulcer of the stomach Portions of the ninth and tenth dorsal areas were involved

by constipation, black stools and loss of weight. Blood had been frequently vomited. Examination showed marked tenderness under both costal margins and in the epigastrium, worse on the right side where pressure caused pain in the back, and hyperalgesia as shown in Figure 14, corresponding to portions of the eighth, ninth and tenth dorsal areas. Case 282 gave a history of pain in the right hypochondrium for six weeks coming on almost immediately after eating, lasting half an hour and accompanied by vomiting, loss of weight, dark colored stools, constipation and weakness. Examination showed tenderness in the right upper quadrant, occult blood in the stools, and hyperalgesia as shown in Figure 15, corresponding to portions of the ninth and

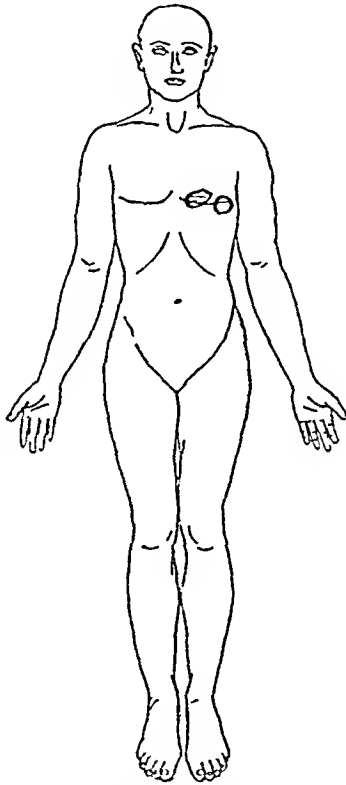


Fig 16—Conditions found in Case 372, hyperalgesia in a case of ulcer of the stomach. The maxima of the fifth and sixth dorsal areas were involved.

tenth dorsal areas. On subsequent admission to another hospital an hour-glass stomach was found at operation. The Wassermann reaction was positive in the blood. The patient in Case 372 had had symptoms at frequent intervals over a period of three years. Pain came on at any time, but particularly at night, was general over the abdomen or in the epigastrium, under the left costal margin or in the back, and was accompanied by nausea and by vomiting which usually gave relief. Examination showed tenderness and resistance in the epigastrium, anemia, and melena. Forty-five minutes after an Ewald meal the gastric contents showed free hydrochloric acid 34, total acid 74 and occult blood present. There was hyperalgesia as shown in Figure 16,

corresponding to the maxima of the fifth and sixth dorsal areas. Operation showed an ulcer of the greater curvature and a carcinoma of the lesser curvature. The segments involved here are much higher than those usually found affected by Head. (The record of the hyperalgesia in this case was unfortunately lost, but the areas shown and drawn from memory are reasonably accurate.)

Carcinoma of stomach. 11 cases, of these seven patients complained of pain, hyperalgesia was found in three cases. Case 372 was discussed above under ulcer of the stomach. Case 40 gave a history of loss of appetite, much pain in the lower abdomen coming on about four hours after meals, some nausea and belching, constipa-

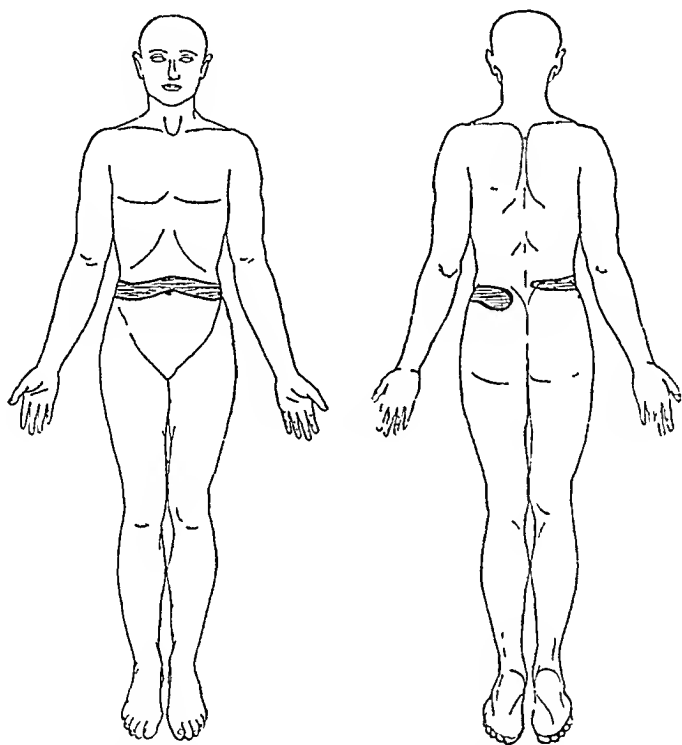


Fig 17—Conditions found in Case 40, hyperalgesia in a case of carcinoma of the stomach. Portions of the tenth and eleventh dorsal areas were involved.

tion and tarry stools, beginning eight or nine months before admission. Examination showed rigidity and tenderness in the upper abdomen, no free hydrochloric acid and a total acidity of only 4, no stasis or melena, and hyperalgesia as shown in Figure 17, corresponding to portions of the tenth and eleventh dorsal areas. At operation a hard nodular crescent-shaped carcinoma was found involving a large part of the stomach and attached to the head of the pancreas. The segments involved here are lower than those given by Head. Possibly this is accounted for by the involvement of the pancreas found at operation. The patient in Case 221 began to feel weak four months before admission, and lost his appetite. He grew constipated, had

sharp pain in the epigastrium radiating upward toward the sternum, vomited at various intervals after his meals, and lost 23 pounds weight. Examination showed a tender fixed mass the size of a hen's egg in the left hypochondrium, no free hydrochloric acid in the stomach contents after an Ewald meal, and hyperalgesia as shown in Figure 18, involving small portions of the ninth dorsal areas in the midline.

Tuberculosis of stomach 1 case, this patient, Case 314, had had pain for fifteen months. Hyperalgesia was not found. The diagnosis made at operation was confirmed at necropsy. No other tuberculous lesions were found.

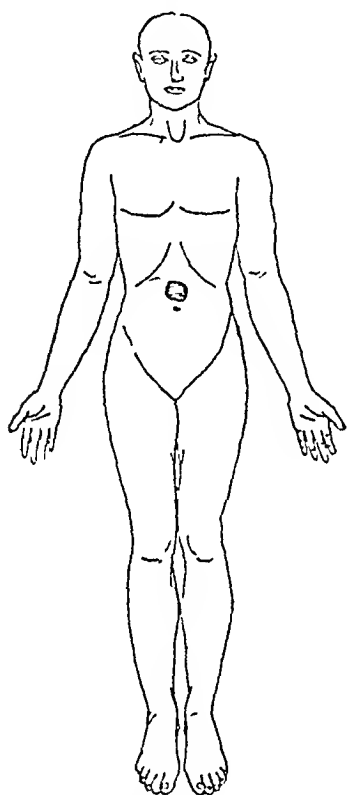


Figure 18

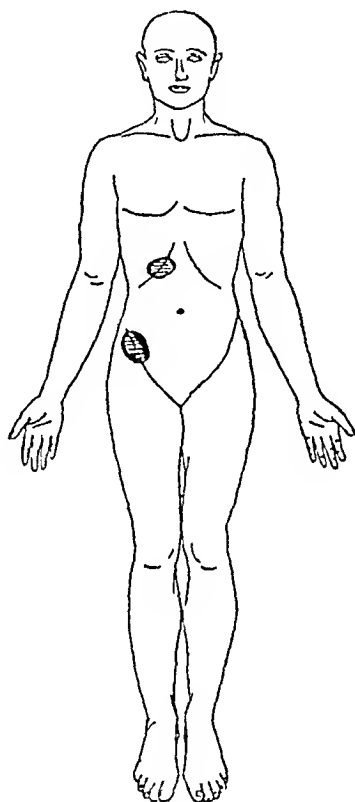


Figure 19

Fig 18—Conditions found in Case 221, hyperalgesia in a case of carcinoma of the stomach. Small portions of the ninth dorsal areas in the midline were involved.

Fig 19—Conditions noted in Case 222, hyperalgesia found in a case of ulcer of the duodenum. The maxima of the eighth and tenth dorsal areas were involved.

Ulcer of duodenum 4 cases, all these patients complained of pain in the epigastrium. Hyperalgesia was found in Case 222. This patient gave a history of attacks of sharp pain under the right costal margin radiating at times all over the abdomen and to the spine, accompanied by nausea, and often relieved by food. Examination showed tenderness at McBurney's point, and slight resistance and tenderness in the region of the pylorus and on Murphy's maneuver. There was hyperalgesia as shown in Figure 19, corresponding approximately to

the maxima of the eighth and tenth dorsal areas. At operation an ulcer of the duodenum was found. The patient subsequently had attacks of pain in the right lower quadrant so that the involvement of the tenth dorsal area may have been due to a chronic appendicitis.

Thus in 25 cases of disease of the stomach, 16 patients, or 64 per cent, complained of pain and 6, or 24 per cent, had hyperalgesia. Of those who had pain 37 per cent showed hyperalgesia. The fifth, sixth, eighth, ninth, tenth and eleventh dorsal areas were found involved.

Abscess of liver. 4 cases, three of these patients complained of pain, hyperalgesia was not found.

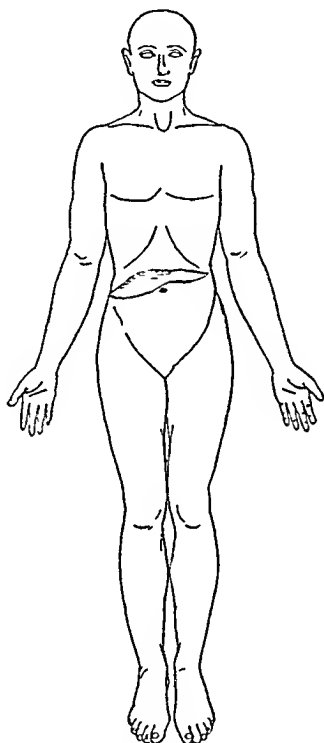


Fig. 20—Conditions noted in Case 81, hyperalgesia found in a case of syphilis of the liver. Portions of the ninth and tenth dorsal areas were involved.

Syphilis of liver. 2 cases, one of these, Case 81, had had pain under the right costal margin and across the upper abdomen for one year with attacks of frequent bowel movements and passage of mucus and some blood. His skin had been darker for two years. Examination showed a small nodule on the surface of an otherwise normal liver, a palpable spleen, mucus in the stools without amebas, and hyperalgesia as shown in Figure 20, corresponding to portions of the ninth and tenth dorsal areas. The Wassermann reaction was positive in the blood and one injection of salvarsan relieved the pain completely.

Carcinoma of liver. 2 cases, both of these patients had pain. The patient in Case 369 had hyperalgesia. He gave a history dating back

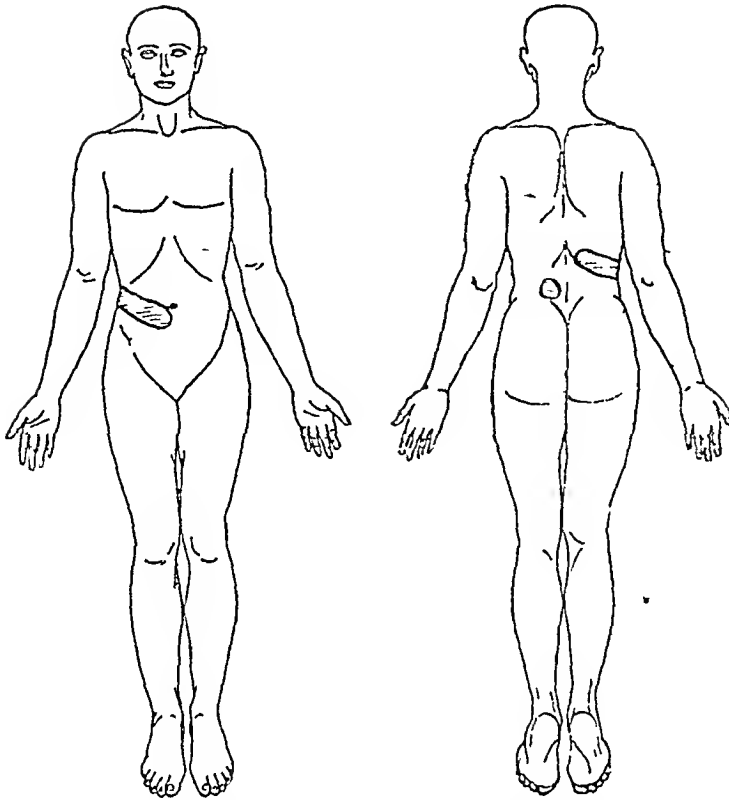


Fig 21—Conditions noted in Case 369, hyperalgesia found in a case of carcinoma of the liver. Portions of the tenth and the maximum of the eleventh dorsal areas were involved.

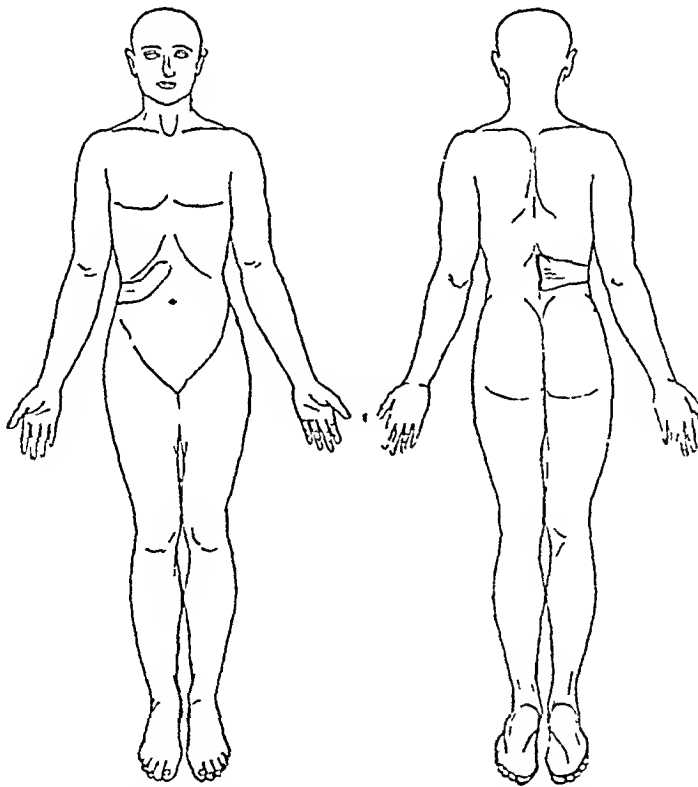


Fig 22—Conditions found in Case 138, hyperalgesia in a case of acute cholecystitis. Portions of the eighth, ninth and tenth dorsal areas were involved.

only ten days, of pain in the right shoulder blade, chest and abdomen, followed by cough, anorexia, and dark colored urine. On examination there was slight jaundice, a much enlarged liver and hyperalgesia as shown in Figure 21, corresponding to a portion of the tenth dorsal area and to the maximum of the eleventh. At operation the liver was found studded with tumor nodules. The involvement of the eleventh dorsal was unexplained unless by spreading or possible metastasis.

Cirrhosis of liver 2 cases, neither of these patients had pain or hyperalgesia.

Cholecystitis, acute 4 cases, two of these were in patients too ill to give any account of themselves. A third had severe pain without

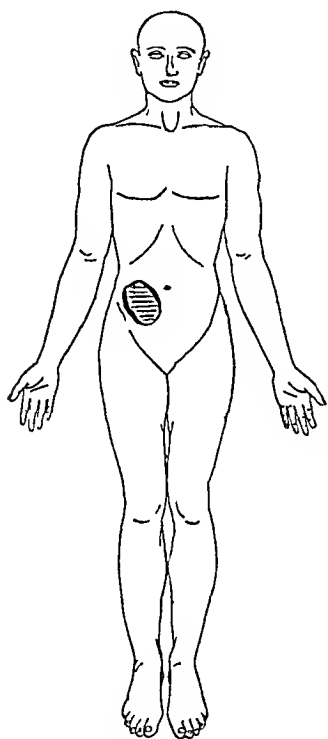


Figure 23

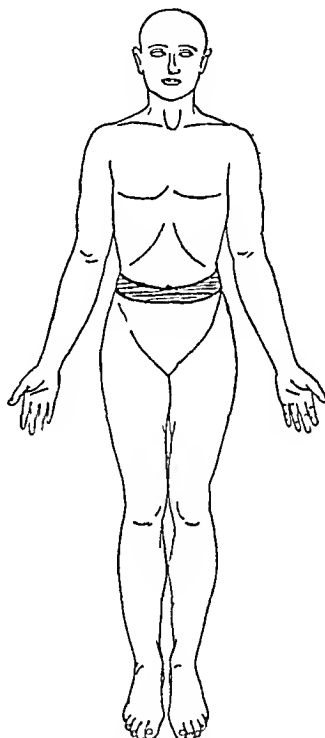


Figure 24

Fig 23—Conditions noted in Case 194, hyperalgesia in a case of cholelithiasis. Portions of the tenth and eleventh dorsal areas were involved.

Fig 24—Conditions found in Case 281, hyperalgesia found in a case of cholelithiasis. A portion of the tenth dorsal area was involved.

hyperalgesia Case 138 was a typhoid patient who developed, during the course of his illness, pain under the right costal margin and hyperalgesia as shown in Figure 22, involving portions of the eighth, ninth and tenth dorsal areas. Nothing very definite could be determined about the gallbladder, but the pain and hyperalgesia were very suggestive of cholecystitis.

Cholecystitis, chronic 1 case, this patient had pain at intervals, hyperalgesia was not found.

Cholelithiasis 7 cases, four complained of pain and of these three had hyperalgesia. Case 194 gave a history of attacks of cramp-like abdominal pain accompanied by nausea, vomiting and sweating, followed by soreness of the abdomen and dating back for years. On examination he was found jaundiced, there was tenderness and rigidity in the region of the gallbladder and the urine contained bile. There was hyperalgesia as shown in Figure 23, rather indistinctly limited and corresponding to portions of the tenth and eleventh dorsal areas. At operation many gallstones were found. Here again a lower dorsal area than that given by Head was found. The patient in Case 281 had had several attacks characterized by intermittent griping pain in the epigastrium, slightly relieved by vomiting and accompanied by

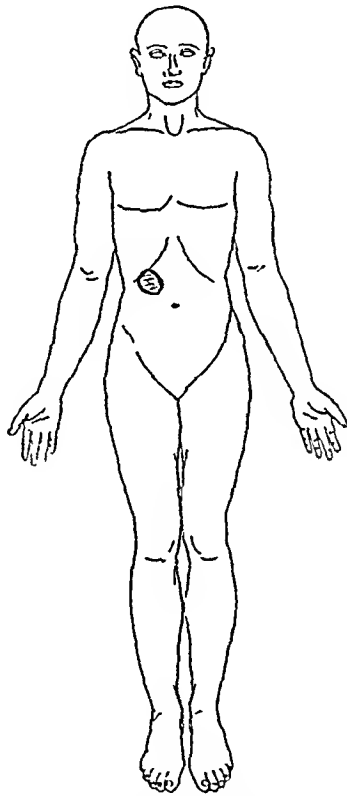


Fig 25—Conditions found in Case 438, hyperalgesia in a case of cholelithiasis. The maximum of the ninth dorsal area was involved.

pain in the right lower quadrant, weakness, nausea, and copious green stools. Examination showed obesity, considerable resistance and tenderness in the region of the gallbladder, slight tenderness at McBunney's point, a temperature of 101, and hyperalgesia as shown in Figure 24, corresponding to a portion of the tenth dorsal area. The patient in Case 438 was a woman of 61 who gave a history of attacks of cramp-like pain in the epigastrium coming on fifteen minutes after meals, radiating to the right and accompanied by nausea. Several months before admission she developed belching and distress after meals with a "numb" feeling in the right lower quadrant. There was

marked tenderness in the region of the gallbladder, less marked tenderness at McBurney's point, and pain on Murphy's maneuver Forty-five minutes after an Ewald meal the stomach contents showed free hydrochloric acid 7, total acid 23 Hyperalgesia was found as shown in Figure 25, corresponding approximately with the maximum of the ninth dorsal area

Hydrops of gallbladder 1 case, this patient, Case 256, had no pain, but came for examination because of a mass on her right side which proved to be a much enlarged and slightly tender gallbladder There was hyperalgesia as shown in Figure 26, corresponding to a point between the maxima of the twelfth dorsal and fourth sacral areas

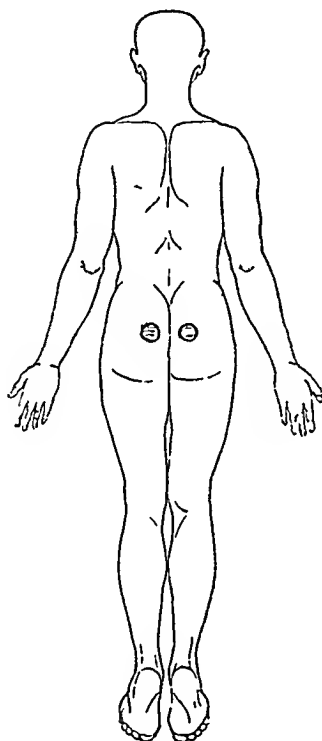


Fig 26—Conditions noted in Case 256, hyperalgesia found in a case of hydrops of the gallbladder A point between the maxima of the twelfth dorsal and fourth sacral areas was involved

Operation was refused and no other cause could be found for the hyperalgesia

Carcinoma of gallbladder 1 case, this patient had neither pain nor hyperalgesia

Carcinoma of common duct 1 case, no pain or hyperalgesia

Catarrhal jaundice 1 case, without pain or hyperalgesia

Cholangitis, acute 1 case, (necropsy finding in a case of carcinoma of the pancreas), pain and hyperalgesia were not noted

Thus in 27 cases of disease of the liver and gall passages, twelve patients, or 44 per cent, had pain, and seven, or 25 per cent, showed

hyperalgesia Of the patients who complained of pain, 58 per cent had hyperalgesia The areas involved were the eighth, ninth, tenth, eleventh (and twelfth?) dorsal areas

Carcinoma of pancreas 1 case, no pain or hyperalgesia

Gastroenteritis, acute 2 cases, this was a necropsy finding in one case In the other it was due to mercuric chlorid poisoning from which the patient afterward died There was abdominal pain without hyperalgesia

Enteritis, acute 1 case, no pain or hyperalgesia

Enterocolitis, acute 1 case, without pain or hyperalgesia

Enteroptosis 4 cases, two patients complained of pain which was attributed in one case to mucous colitis, hyperalgesia was not found

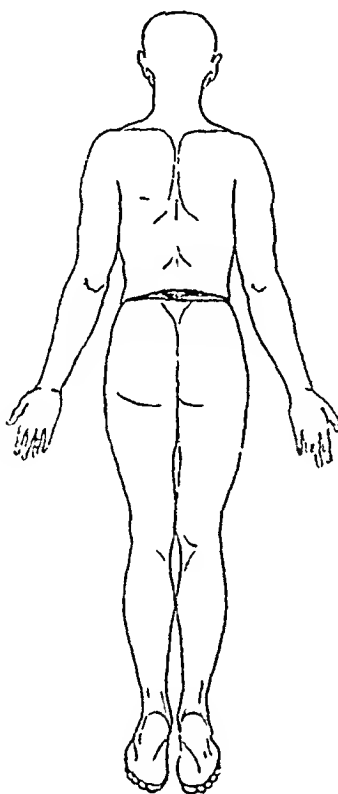


Fig 27—Conditions found in Case 156, hyperalgesia in a case of acute appendicitis The posterior portion of the eleventh dorsal area was involved

Intestinal neurosis 1 case, without pain or hyperalgesia

Tuberculosis of intestines 2 cases, one of these patients was in a stupor when admitted and made no complaint One had vague left-side abdominal pain without hyperalgesia The lesions were demonstrated at necropsy in both cases

Appendicitis, acute 6 cases, pain was pronounced in each of these, hyperalgesia was found in one This patient, Case 156, gave a history of severe general abdominal pain for three days, with constipation, chills, fever, sweats, and aching pain in the head and back Examination showed at first only slight tenderness at McBurney's point, later a

small mass and hyperalgesia as shown in Figure 27, corresponding with the posterior portion of the eleventh dorsal area. At operation an abscess was found about the appendix.

Appendicitis, chronic 11 cases, one of these patients, Case 438, already discussed under cholelithiasis, complained of "numbness" in the right lower quadrant where tenderness was found at McBurney's point. Nine patients complained of pain, which was, in five cases, in the right lower quadrant, in four cases, in the epigastrium. Hyperalgesia was found in three cases. Case 155 gave the unusual history of pain under the sternum on swallowing, inability to eat solid food, and constant distress in the upper abdomen. There was some tender-

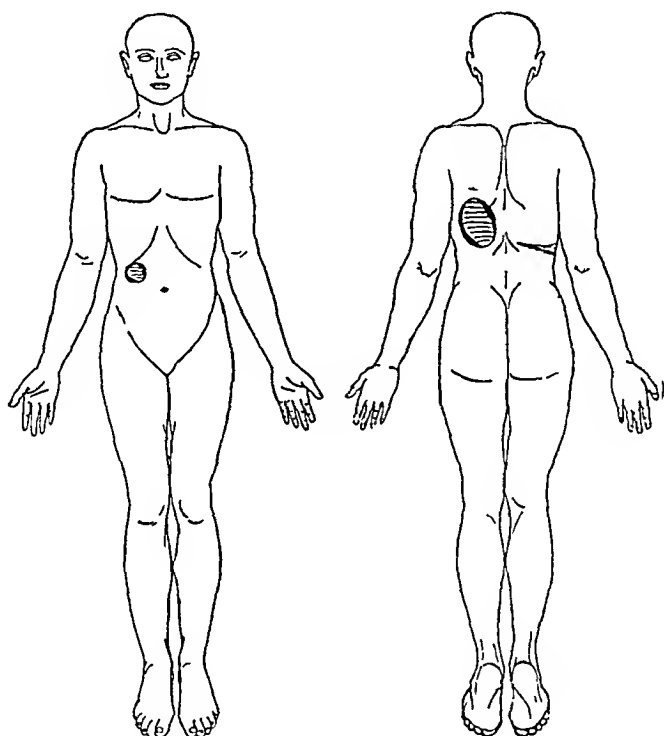


Fig 28—Conditions noted in Case 155, hyperalgesia found in a case of chronic appendicitis. The maximum anteriorly and a portion posteriorly of the ninth dorsal area were involved.

ness in the region of the gallbladder and hyperalgesia as shown in Figure 28, corresponding with the maximum anteriorly and a portion posteriorly of the ninth dorsal area on the right. Portions of the sixth, seventh, eighth and ninth dorsal areas posteriorly on the left were also involved. It was thought that a chronic cholecystitis might be the cause of the pain. On opening the abdomen, the gallbladder was found normal but the appendix was chronically inflamed. Its removal relieved the patient of all his symptoms. Although the ninth dorsal area receives sensory fibers from the intestine, reference of the pain and hyperalgesia to a point so far removed as the sixth dorsal area

seems difficult to explain except by "spreading" The patient in Case 165 had had pain in the right lower quadrant at intervals for three years, accompanied by fever and chills and usually by belching Examination showed marked tenderness over the appendix and hyperalgesia as shown in Figure 29, corresponding rather closely with the tenth dorsal area The third patient, Case 166, gave a history of distress after eating, belching, anorexia, nausea, and finally of griping pain and burning in the epigastrium, worse after meals There was tenderness and resistance at McBurney's point and indefinite hyperalgesia as shown in Figure 30, corresponding to a portion of the tenth dorsal area

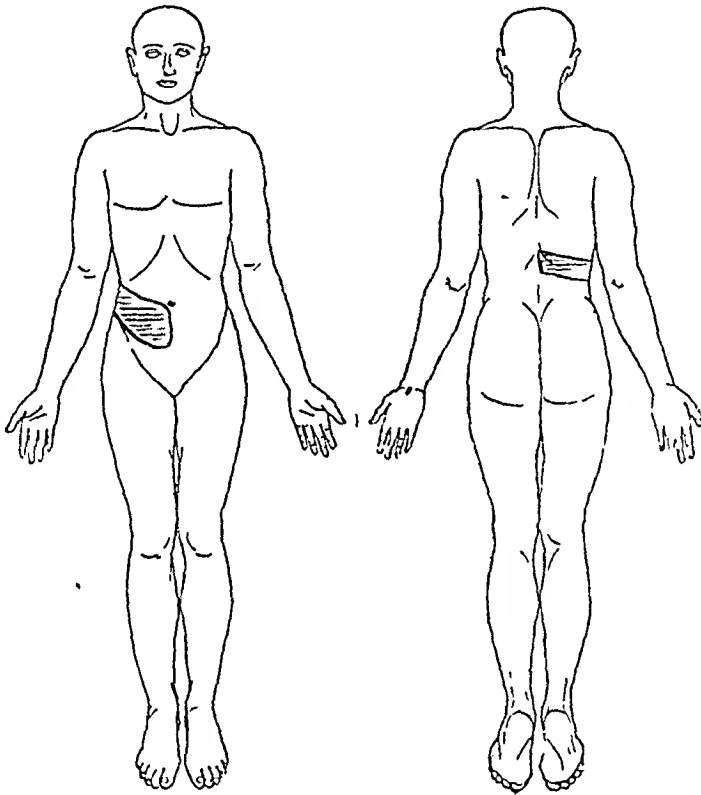


Fig 29—Conditions noted in Case 165, hyperalgesia found in a case of chronic appendicitis The area involved corresponded rather closely with the tenth dorsal

Tuberculosis of appendix 1 case, Case 252 this patient was a young student who, as long as he could remember, had had dull pain in the lower abdomen especially aggravated by defecation At times there had been sharp pain in the right lower quadrant On examination tenderness was found in the region of the appendix and over the sigmoid There was hyperalgesia as shown in Figure 31, corresponding to the maxima of the twelfth dorsal areas Operation some months later showed tuberculosis of the appendix

Tuberculosis of cecum 1 case, this patient was uremic on admission and the lesion was found only at necropsy There was a history of pain in the epigastrium

Colitis, acute 5 cases, this was found in each instance only at necropsy One patient had had colicky pain in the abdomen for a month but frequent stools only for five days before admission There was no hyperalgesia

Colitis, chronic 7 cases, two of these patients complained of pain in the epigastrium, hyperalgesia was not found

Constipation This was associated with large amounts of mucus in the stools in two cases, one patient having pain in the epigastrium In seven cases it was the main or only diagnosis Three of these latter patients complained of pain but did not show hyperalgesia In Case 7, hyperalgesia was found without complaint of pain The his-

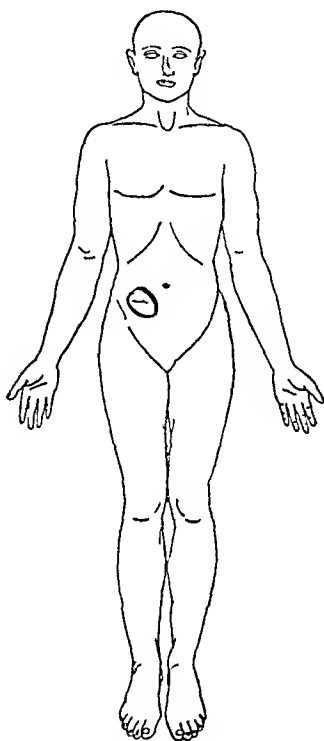


Figure 30

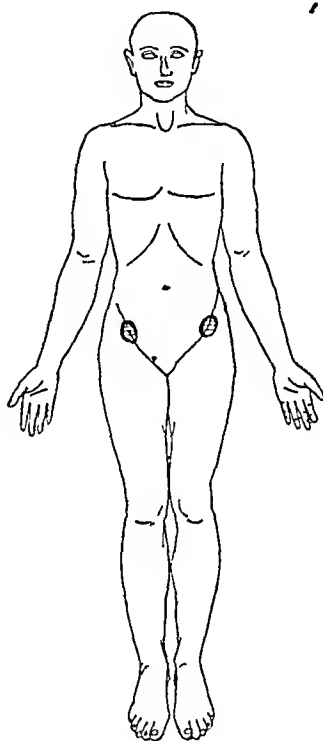


Figure 31

Fig 30—Conditions noted in Case 166, hyperalgesia found in a case of chronic appendicitis A portion of the tenth dorsal area was involved

Fig 31—Conditions noted in Case 252, hyperalgesia found in a case of tuberculosis of the appendix The maxima of the twelfth dorsal area were involved

tory was of fulness after eating, palpitation, headache, and a film over the eyes Hyperalgesia was found as shown in Figure 32, corresponding approximately to the maxima of the tenth and of the sixth dorsal areas Examination was otherwise negative and daily bowel movements gave him complete relief

Dysentery, entamebic 3 cases, two of these patients complained of pain, hyperalgesia was not found

Thus in fifty-one cases of disease of the small and large intestines, twenty-seven, or 52 per cent, had pain, and six, or 11 per cent, had hyperalgesia. Of the patients who complained of pain, 22 per cent showed hyperalgesia. The (sixth, seventh, eighth?), ninth, tenth, eleventh and twelfth dorsal areas were involved.

Peritonitis, acute, general 3 cases, this was terminal in two patients who were too ill to give any account of themselves. In a third there was right-side abdominal pain without hyperalgesia.

Tuberculosis of peritoneum 2 cases, both of these patients had pain in the upper abdomen without hyperalgesia.

Peritonitis, pelvic 1 case, no pain or hyperalgesia.

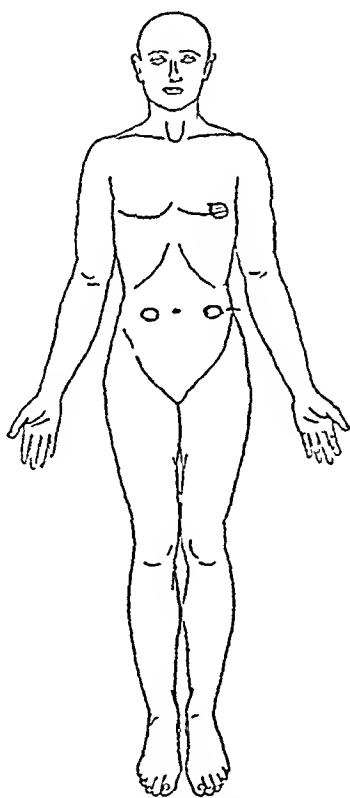


Fig 32—Conditions noted in Case 7, hyperalgesia found in a case of constipation. The maxima of the tenth and sixth dorsal areas were involved.

Prostatitis, acute 1 case, this patient had pain on urination but no hyperalgesia over the sacral areas (discussed under pyelitis).

Prostatitis, chronic 2 cases, without pain or hyperalgesia.

Pyelitis 2 cases, this was a necropsy finding in one patient who entered in uremia and was found to have an ascending nephritis. Case 265 gave a history of slight pain in the left lower back for several days one year before. Four days before admission this pain returned with chilly sensations, fever, anorexia, frequent and painful urination and a urethral discharge. On examination there was some muscular spasm on the left side of the abdomen, pain on bimanual palpation of the left kidney, tenderness in the left costovertebral angle and

moderate elevation of temperature to 101. The prostate was found enlarged and its secretion purulent. Pus was found in the urine from both ureters. Roentgenologic examination was negative for stone. Phenolsulphonephthalein appeared from the right ureter in three minutes, but on the left it had not appeared in forty minutes. Guinea-pigs were injected but were not found tuberculous. There was hyperalgesia as shown in Figure 33, involving portions of the tenth, eleventh and twelfth dorsal areas. As will be seen in other records this hyperalgesia was found rather characteristic for disease of the kidney and ureter.

Tuberculosis of kidney 1 case, this patient had had pain in the right lower quadrant, there was no hyperalgesia.

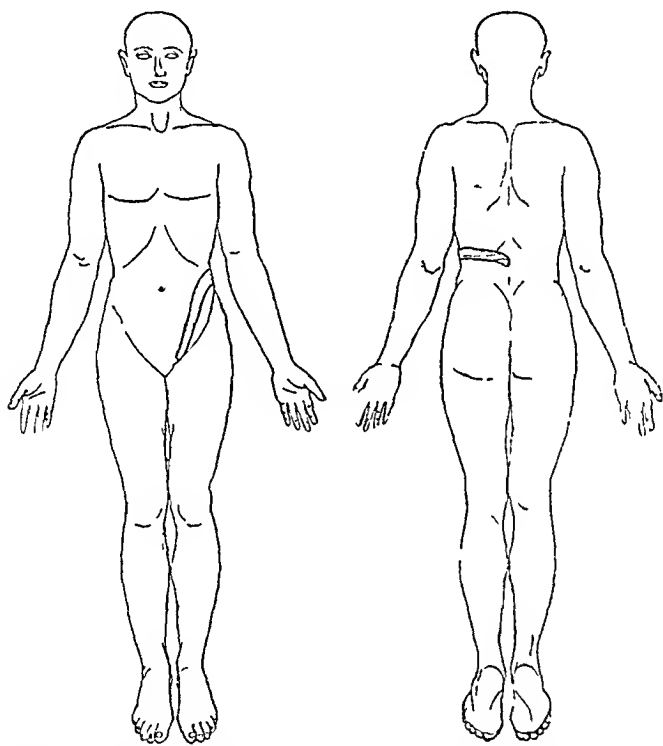


Fig 33—Conditions found in Case 265, hyperalgesia found in a case of pyelitis. Portions of the tenth, eleventh and twelfth dorsal areas were involved.

Nephrolithiasis 5 cases, all these patients had pain, three had hyperalgesia. The patient in Case 247 had had three attacks of severe sharp pain on the left side in the region of the tip of the twelfth rib, accompanied by sweating, vomiting and anuria and followed by the passage of normal urine in twenty-four hours. The last attack came four days before admission. Examination showed tenderness in the region of both kidneys but especially marked on the left, and hyperalgesia as shown in Figure 34, corresponding approximately to the lateral maximum of the tenth dorsal area. The urine contained pus, and staphylococci were found in smears and grown in pure culture.

from a catheterized specimen. The bladder wall was slightly inflamed. A ureteral catheter entered the left ureter 15 cm but no farther, and carentos could not be injected beyond this point. Roentgenologic examination showed a shadow 1 cm in diameter at the tip of the transverse process of the third lumbar vertebra on the left side. The patient in Case 251 had had slight tenderness in the left side of the abdomen for two years. One week before admission he developed pain in the left flank radiating into the scrotum, with tenderness in the left lumbar region. There was considerable tenderness extending from the left costovertebral angle to the left lower quadrant, slight elevation of temperature to 99.2, many red blood cells in the urine and hyperalgesia as shown in Figure 35, involving portions of the tenth,

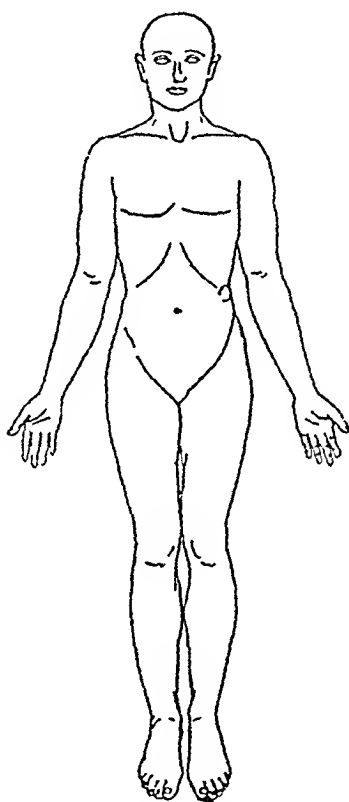


Fig 34—Conditions found in Case 247, hyperalgesia found in a case of nephrolithiasis. The maximum of the tenth dorsal area was involved.

eleventh and twelfth dorsal areas. Cystoscopy showed a small stone projecting from the end of the ureter. The patient in Case 389 gave a history of pain in the back following a gonorrheal urethritis fourteen years before. Two days before admission he had pain in the right lower quadrant with nausea, fever, chills and soreness of the abdomen. There was also complaint of headache, spots before the eyes, and dyspnea on exertion. Examination showed a heavy cloud of albumin, a large number of granular casts and a few white blood cells in the urine, but was otherwise negative. Two weeks after admission there was severe pain in the left flank and testicle and hyperalgesia as shown

in Figure 36, corresponding approximately with the lateral maximum of the tenth dorsal area. The Roentgen ray showed probable stone in the right kidney. Cystoscopy and ureteral catheterization gave negative results and a culture of the urine remained sterile. The patient in Case 300 had had dull aching pain in the left flank for three years and soreness just below the umbilicus somewhat relieved by defecation. Both these conditions had been much relieved by a tight binder. For six months before admission she had had every few weeks attacks of sudden distress in the epigastrium after food but was not relieved by the vomiting which followed. The patient was of the type of congenital asthenia described by Stiller. The tonsils were

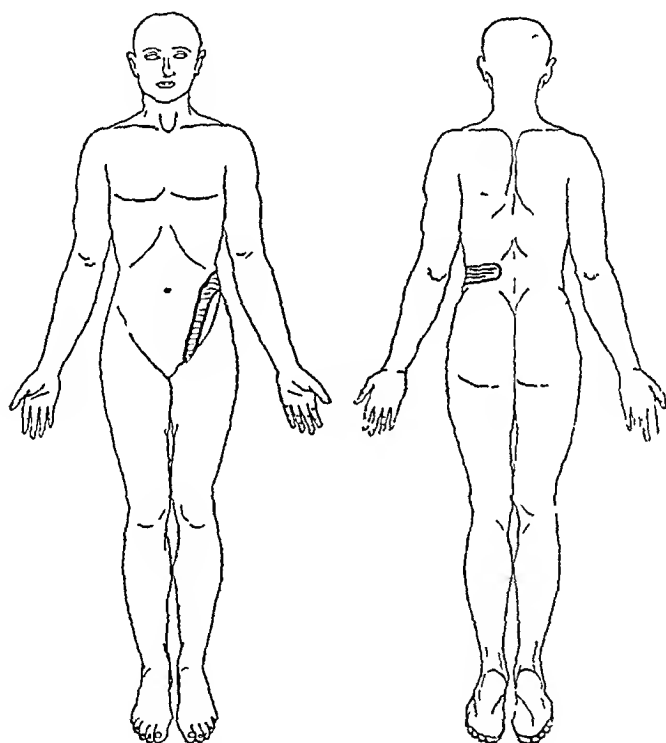


Fig 35—Conditions noted in Case 251, hyperalgesia found in a case of nephrolithiasis. Portions of the tenth, eleventh and twelfth dorsal areas were involved.

enlarged, there were some changes at the right apex, both kidneys were movable to the third degree, and there was general abdominal tenderness especially marked in the left flank, over the colon and above the pubes. Hyperalgesia was found as shown in Figure 37, corresponding to that previously described (tenth, eleventh, twelfth dorsal) and including, in addition, portions of the seventh, eighth and ninth dorsal areas posteriorly. These latter were not found by Head to be involved in disease of the kidney. Further investigation to determine the cause of this pain and hyperalgesia were unfortunately not carried

out because following tonsillectomy, a forced diet and a proper abdominal belt there was a gain in weight and no further complaint

Nephroptosis 3 cases, none of these patients had pain which could be attributed to this condition, with the possible exception of the patient in Case 300 just discussed

Thus in 11 cases of disease of the kidney and ureters, 7, or 63 per cent, had pain and 5, or 45 per cent, showed hyperalgesia. Of those patients who had pain, 71 per cent had hyperalgesia.

Cystitis, acute 1 case, this patient had pain without hyperalgesia.

Cystitis, subacute 1 case, without pain or hyperalgesia.

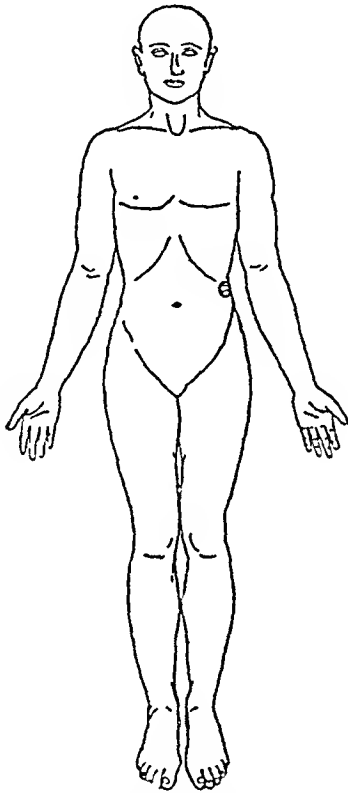


Fig 36—Conditions noted in Case 389, hyperalgesia found in a case of probable nephrolithiasis. The maximum of the tenth dorsal area was involved.

Cystitis, chronic 2 cases, without pain or hyperalgesia referable to bladder. One of these cases, Case 247, was discussed under nephrolithiasis.

Salpingitis, acute 1 case, there was marked pain here without hyperalgesia.

Arthritis deformans of spine 7 cases, these cases were grouped together because in several of them pain was attributed by the patient to visceral disease. In this group, six patients complained of pain, which was abdominal in two cases, in the back in three cases and in the hip and leg in one case. There was hyperalgesia in three of these cases. Case 98 gave a history of pain in the left buttock, thigh and leg occurring only on motion of the leg. On examination there was

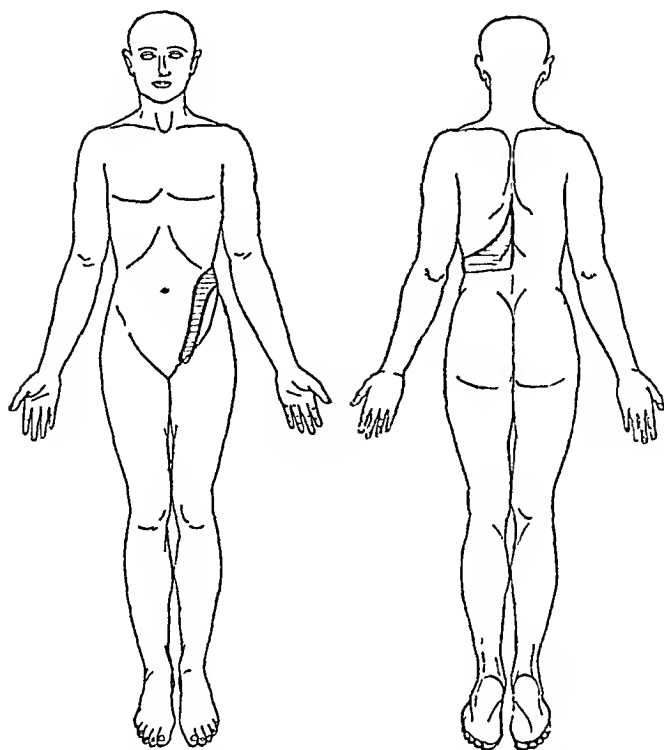


Fig 37—Conditions noted in Case 300, hyperalgesia found in a case of possible nephrolithiasis. Portions of the seventh, eighth, ninth, tenth, eleventh and twelfth dorsal areas were involved.

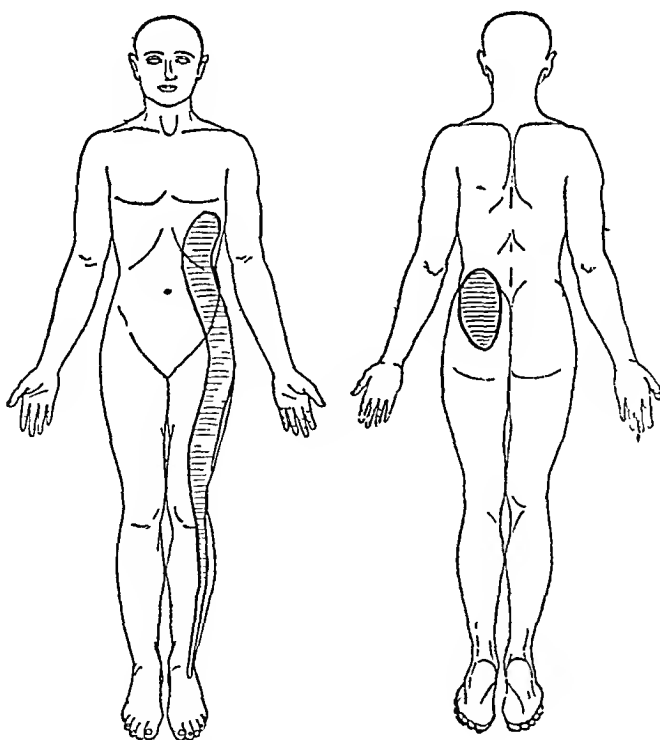


Fig 38—Conditions noted in Case 98, hyperalgesia found in a case of arthritis deformans of the spine. Portions of the dorsal areas from the sixth to the twelfth and of the second, third, fourth and fifth lumbar areas were involved.

tenderness to pressure over the lower lumbar vertebrae and upper sacrum, some pain on hyperextension of the lumbar spine, and all movements of the spine were slightly limited. Roentgenographic examination showed osteoarthritis of the lumbar spine, lateral displacement to the left of the fourth and fifth lumbar vertebrae and apparent bony union of the two vertebrae on the left side. There was hyperalgesia as shown in Figure 38, involving portions of the dorsal areas from the sixth to the twelfth passing through the second, third and fourth lumbar areas, to which visceral pain is not referred, and terminating in the fifth lumbar area. Posteriorly the hyperalgesia

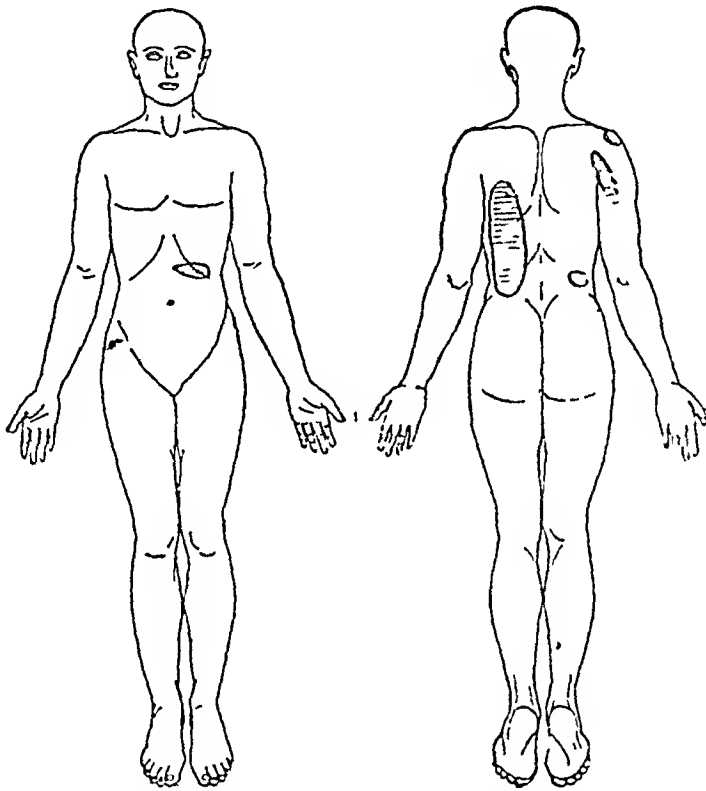


Fig 39 —Conditions noted in Case 83, hyperalgesia found in a case of syphilitic infection of long standing. Portions of the sixth, seventh, eighth, ninth and tenth, and the maximum of the eleventh dorsal areas were involved. No special organ could be accused.

involved principally the eleventh and twelfth dorsal areas. Careful examination failed to reveal any visceral disease to which this hyperalgesia could have been attributed. This case may serve as a type of the other cases showing hyperalgesia as a result of vertebral disease.

Syphilis. Of 54 cases of syphilitic infection only six patients had pain which could not be traced to one of the viscera. Three of these patients showed hyperalgesia. Case 83 gave a history of sudden diplopia a week before, followed in twelve hours by sharp pain in the left shoulder radiating to the chest and right shoulder, with some headache, vomiting and loss in weight. There was a paralysis of the right superior oblique, some chronic lung changes, muscular resistance on

the right side of the abdomen, absence of Achilles reflexes and hyperalgesia as shown in Figure 39, corresponding anteriorly to a portion of the eighth, posteriorly on the left to portions of the sixth, seventh, eighth, ninth and tenth and on the right approximately to the maximum of the eleventh dorsal areas. Two small hyperalgesic areas occur in the areas to which visceral pain is not referred. The spinal fluid contained 30 cells per cubic millimeter, increased globulin and albumin, but the Wassermann reaction was negative both in the blood and in the spinal fluid. He was much relieved by an injection of salvarsan. This case is perhaps an instance of so-called "spreading," the cause of the original disturbance being possibly an alcoholic gastritis. The

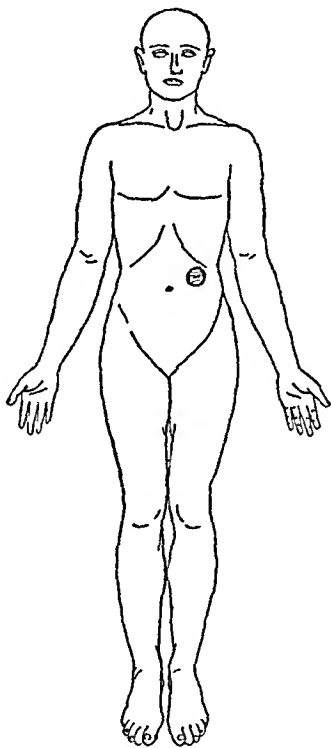


Fig. 40—Conditions noted in Case 404, hyperalgesia found in a case of syphilitic infection. The maximum of the ninth dorsal area was involved. Probably the stomach was the cause of the referred pain.

patient in Case 404 had had sharp burning pain in the left upper quadrant after meals for five years, with belching, constipation, pain in head and shoulders and loss of weight. A gastro-enterostomy had given him some relief, but his symptoms returned. On admission there were two laparotomy scars above the umbilicus and hyperalgesia as shown in Figure 40, corresponding approximately to the maximum of the ninth dorsal area. The Wassermann reaction was positive and one injection of salvarsan relieved all his symptoms. The patient in Case 71 had had severe knife-like pain under the left costal margin coming on a week previously with "unconsciousness" and lasting

almost an hour. A year before he had had a similar attack. On admission he still had severe pain in the same situation. There was a pigmented line on the gums about the incisors (probably racial), considerable arterial thickening, a palpable spleen, no stippling of the red blood cells and a positive Wassermann reaction in the blood. Abdominal massage brought on severe pain which was almost immediately controlled with atropin. There was hyperalgesia as shown in Figure 41. One injection of salvarsan gave him much relief.

Functional diseases. There were twelve patients in whom a sufficient cause could not be found to explain the symptoms. Of these, five complained of pain, one showing hyperalgesia. This patient, Case 274,

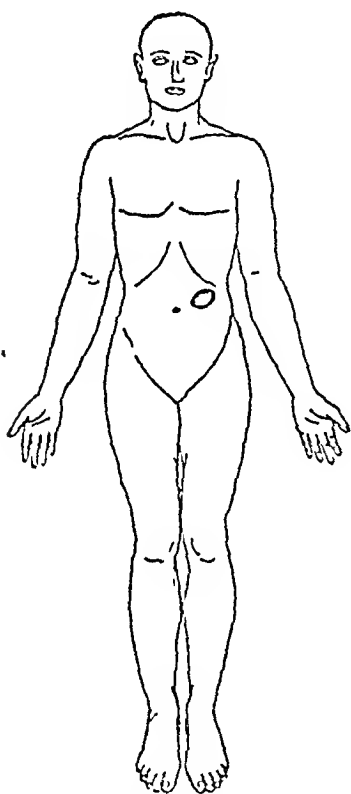


Figure 41

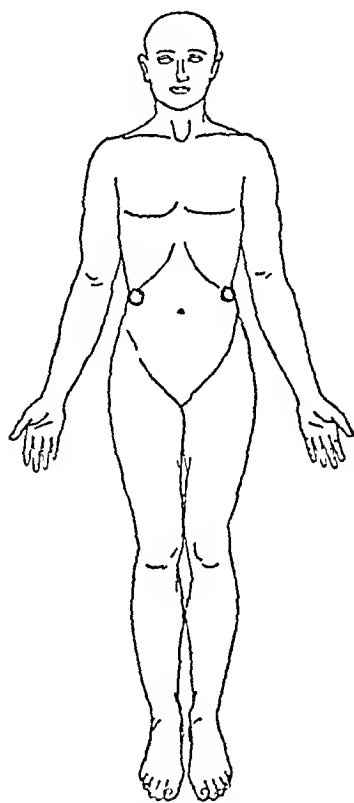


Figure 42

Fig 41—Conditions noted in Case 71, hyperalgesia found in a case of abdominal syphilis. The maximum of the ninth dorsal area was involved.

Fig 42—Conditions noted in Case 274, hyperalgesia found in a case of functional disease. The maxima of the tenth dorsal area were involved.

gave a history of lumbar pain, pain in the limbs, weakness, palpitation, vomiting, nervousness and dizziness. He felt oppressed in heated rooms and in the presence of other people. Examination was negative except for hyperalgesia as shown in Figure 42, involving the maxima of the tenth dorsal areas. One patient in this group, Case 59, had hyperalgesia without pain. He was a man of 40 who complained of attacks of palpitation, dyspnea, headache and frequent urination which he had had from the age of 13. Except for some asymmetry of the

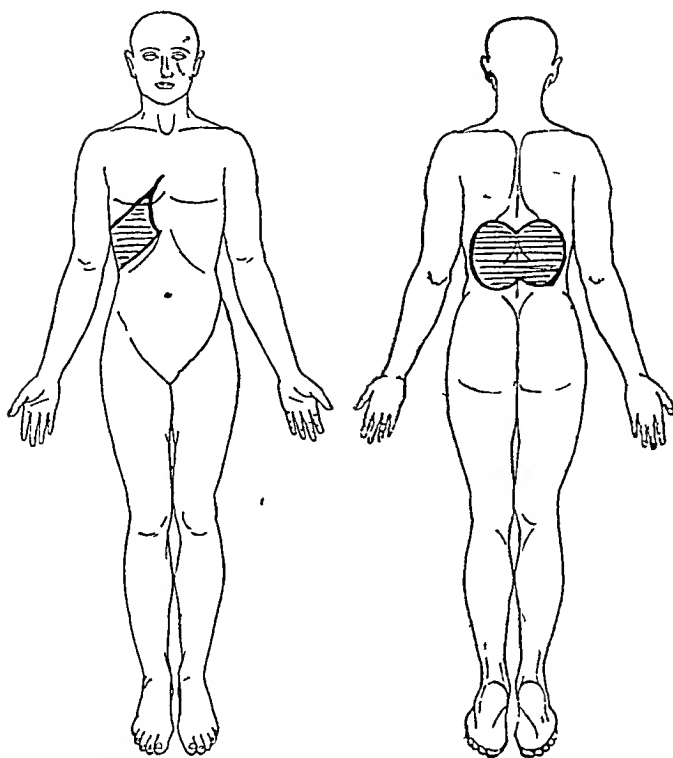


Fig 43—Conditions noted in Case 59, hyperalgesia found in a case of functional disease. Portions of the sixth, seventh, eighth, ninth and tenth dorsal areas were involved.

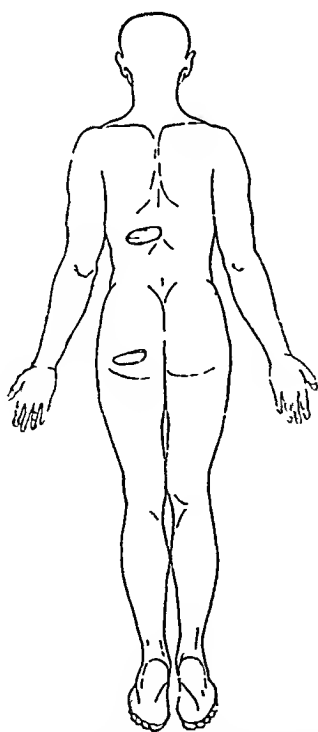


Fig 44—Conditions noted in Case 244, hyperalgesia corresponding to portions of the eighth, ninth and tenth dorsal and second sacral areas could not be explained.

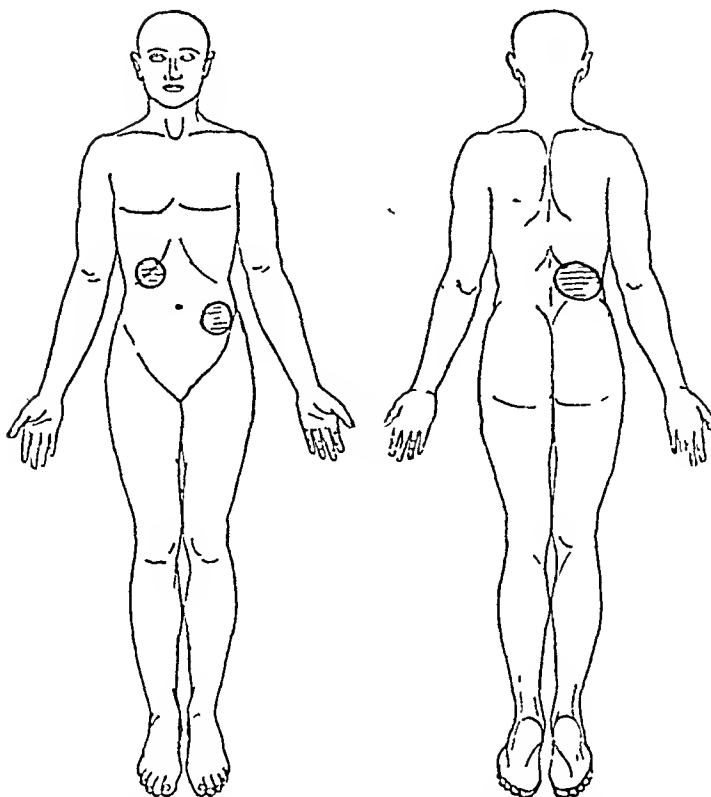


Fig 45—Conditions noted in Case 127, hyperalgesia corresponding to the maximum of the ninth, and portions of the tenth and eleventh dorsal areas could not be explained

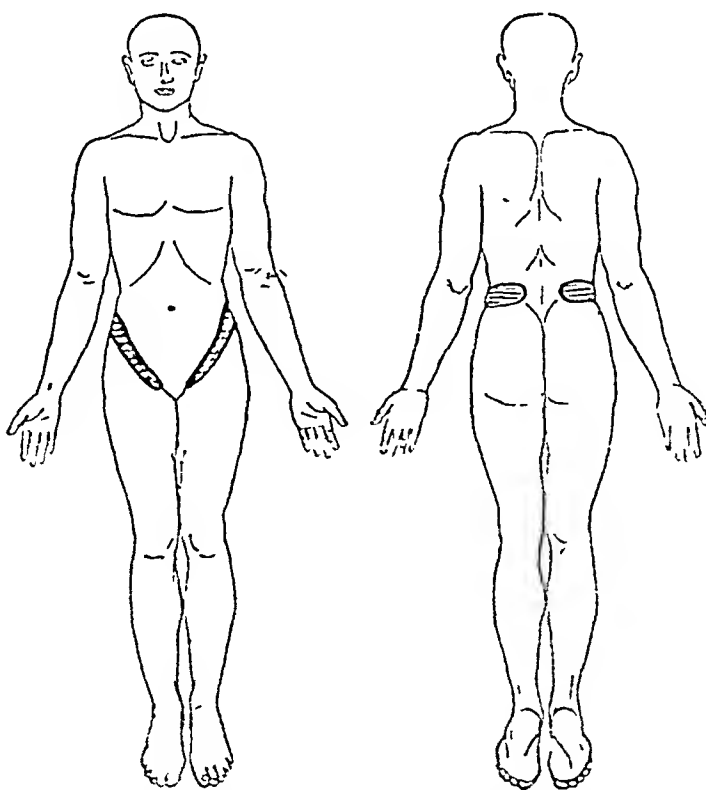


Fig 46—Conditions noted in Case 406, hyperalgesia corresponding to the eleventh dorsal areas on both sides could not be explained

chest, examination was negative. There was hyperalgesia as shown in Figure 43, involving portions of the sixth, seventh, eighth, ninth and tenth dorsal areas. He was much relieved by a cantharides blister on his spine.

Typhoid Fever 6 cases, four of these patients had pain, hyperalgesia was found in one case, Case 138, discussed under cholecystitis.

Unexplained 4 cases. Case 244 gave a history of painful swelling of the great toe with some pain in the hip, sweating, lassitude, and loss in weight. On examination there were tophi in the ears, a few wheezy râles over the right upper chest, fibrillating auricles, some redness and swelling of the great toe on the right, crepitations of the knee joints.

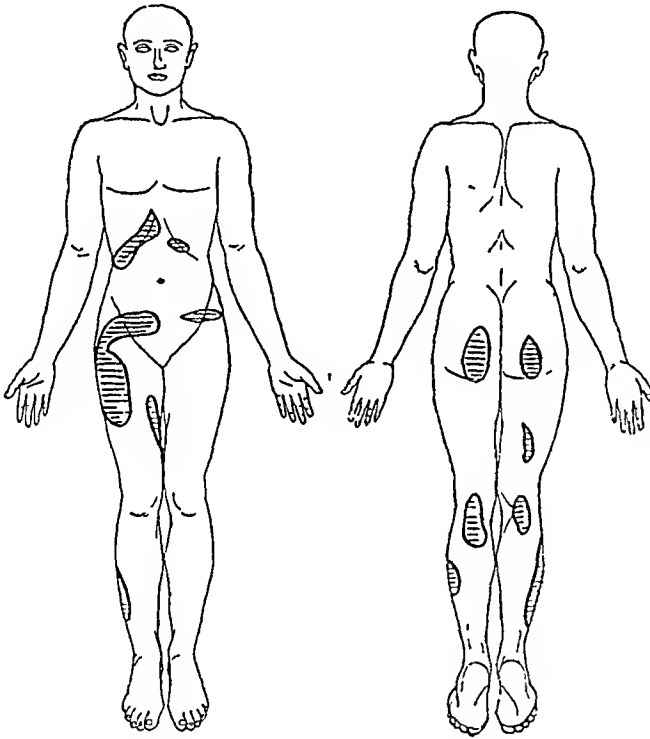


Fig 47—Conditions noted in Case 107, hyperalgesia corresponding to portions of the seventh, eighth, ninth, eleventh and twelfth dorsal, first lumbar, and second, third and fifth sacral areas could not be explained.

and hyperalgesia as shown in Figure 44, corresponding to portions of the eighth and ninth dorsal and a portion of the second sacral areas. The patient in Case 127 had had shortness of breath and a sense of pressure under the sternum for two months, and transient blurring of vision for three years. On examination there was Cheyne-Stokes breathing, a coated tongue, rather marked arterial thickening, a blood pressure of 200 mm Hg, a few râles at the right base and tenderness to the left of the umbilicus and in the costovertebral angles. The urine contained much albumin, many casts and a few white blood cells. There was nephritic edema of the fundi oculi. Hyperalgesia was

found as shown in Figure 45, corresponding to the maximum of the ninth, and portions of the tenth and eleventh dorsal areas. A roentgenogram of the kidney was negative for stone and the hyperalgesia remained unexplained. Case 406 gave a history beginning four months before of dizziness and weakness coming on in attacks, attributed to eating meat or potatoes, or drinking milk, and accompanied by nausea and gradually by some loss in weight. There was very slightly diminished hearing on the right and slight generalized abdominal tenderness on physical examination. Ear tests showed the caloric absent on the right and spontaneous rotary nystagmus to the right. On turning to the right there was nystagmus for fifteen seconds rotatory to the right, on turning to the left there was nystagmus for thirty seconds rotatory to the right. The cochlea was intact on both sides. The diagnosis was neuritis of the vestibular branch of the eighth cranial nerve. There was hyperalgesia as shown in Figure 46, corresponding approximately to the eleventh dorsal area on both sides, for which careful examination failed to reveal any cause. The patient in Case 107 had had belching, sour eructations, heaviness in the epigastrium, rumbling in the head, dizziness and weakness following a blow on the head three months before admission. Examination showed slight deafness on the left, some muscular resistance in the epigastrium and pronated feet. The hemoglobin was 68 per cent. Roentgenologic examination showed possible adhesions about the pylorus. Hyperalgesia was found as shown in Figure 47, involving portions of the seventh, eighth, ninth, eleventh and twelfth dorsal, first lumbar, second, third and fifth sacral areas. No cause was found for this extensive involvement.

CONCLUSIONS

In this series of 460 hospital cases, hyperalgesia was a frequent finding in visceral disease.

In diseases of the lungs hyperalgesia was found in 3 per cent of the cases, or in 13 per cent of those who complained of pain.

In diseases of the heart and aorta, hyperalgesia was found in 7 per cent of the cases, or in 18 per cent of those who complained of pain.

In diseases of the stomach, hyperalgesia was found in 24 per cent of the cases, or in 37 per cent of those who complained of pain.

In diseases of the liver and gall passages, hyperalgesia was found in 25 per cent of the cases, or in 58 per cent of those who had pain.

In diseases of the intestines hyperalgesia was found in 10 per cent of the cases or in 22 per cent of those who had pain.

In diseases of the kidney and ureters hyperalgesia was found in 45 per cent of the cases, or in 71 per cent of those who complained of pain.

Whole dorsal areas as outlined by Head were rarely found, but certain maxima were frequently found

The large number of areas over which hyperalgesia may be found in disease of each viscus, and the number of viscera supplied by each segment, made hyperalgesia of practically no importance in diagnosis with the possible exception of diseases of the kidney in which it had a somewhat characteristic form *

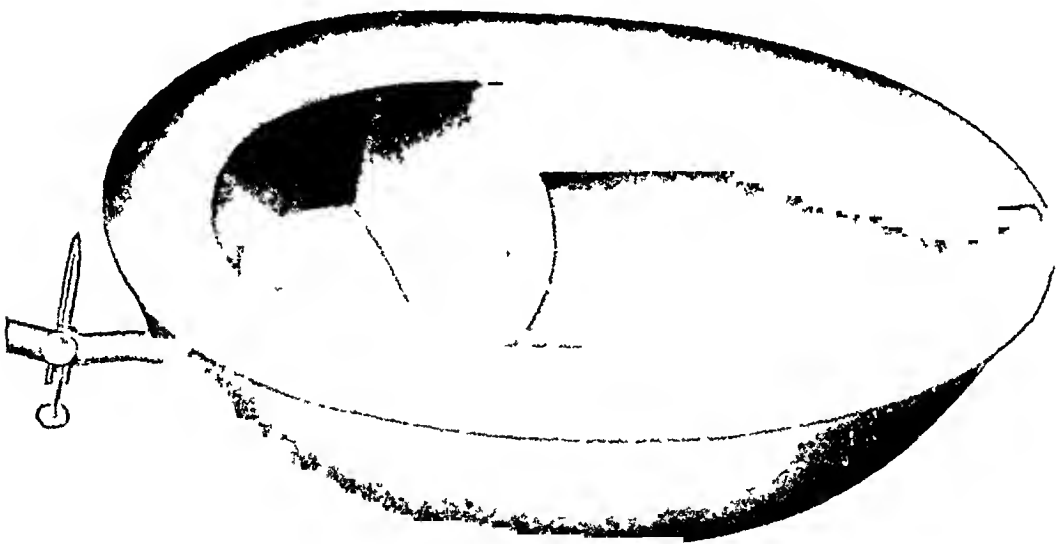
240 Stockton Street

* This investigation was carried on in the medical wards of Lane Hospital, Leland Stanford Jr University Medical School. Permission to report the cases is due to the kindness of Dr R L Wilbur, dean

AN APPARATUS FOR THE QUANTITATIVE COLLECTION OF URINE FROM WOMEN

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The difficulty, in fact, we may almost say the practical impossibility, of obtaining accurate twenty-four-hour quantities of urine from female hospital patients has probably been recognized by every investigator who has attempted to conduct metabolism experiments on this class of subjects. Our own experience has been that even when under the constant supervision of competent nurses, intelligent female patients (particularly when under the influence of cathartics) will frequently lose from 5 to 25 per cent of the daily amount of urine.



Apparatus for quantitative collection of urine from women

In order to overcome this difficulty we have devised a "divided pan," an illustration of which is shown. This pan, which is made of sheet copper, nickel plated, is constructed along the lines of the ordinary hospital bed pan, being 14 inches long by $9\frac{3}{4}$ inches wide, the front end is $4\frac{1}{4}$ inches high, the back $9\frac{1}{2}$ inches, $6\frac{1}{4}$ inches from the front end is a curved slanting partition which divides the vessel into two chambers, one for the reception of urine, the other for feces. The front or urine compartment is provided with an outlet consisting of a short piece of copper tubing half an inch in diameter and closed by means of a piece of rubber tubing and a pinchcock. The top of the pan is so constructed that it may be easily removed for cleaning.

We have now had this apparatus in use for many months in the women's and children's wards of the Massachusetts General Hospital, during which time it has been used by a large number of patients with practically invariable success. It may be used in bed with the subject in the recumbent position, or in the case of patients well enough to be up and about the ward, may be placed on a low stool.

While the device was introduced primarily for our metabolism experiments, it has been found useful in many cases in the routine collection of urine or feces, particularly in the case of very stupid patients and those unable to speak English.

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THE BACTERIAL FLORA OF LYMPHATIC GLANDS^{*}

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That the regional lymphatic glands can filter out bacteria from an infected area has been conclusively shown with reference to numerous organisms by simultaneously cultivating them from both situations. More generalized invasion of glands in agonal and postagonal states is also a matter of common experience, many special studies having been made on this point, among which may be mentioned the recent ones of Southard and Canavan.¹ In certain specific diseases, furthermore, the causal organisms may be present in the glands in association with the characteristic changes—notably in tuberculosis. Within the last two years, a great deal of interest has arisen in the latter type of gland infection, stimulated especially by bacteriologic studies of Hodgkin's disease, and other conditions associated with glandular enlargements of obscure origin.

Bunting and Yates,² in 1913, almost simultaneously with Negri and Mieremet,³ isolated in pure culture by aerobic methods, from the lymph nodes of patients in three cases of Hodgkin's disease, a pleomorphic diphtheroid bacillus. In two other cases, the organism was recognized, but not secured in pure culture. Bunting and Yates felt that they were probably dealing with the same organism described by Negri and Mieremet in two cases,³ and possibly with the bodies demonstrated morphologically by Fraenkel and Much,⁴ in 1910. In spite of the frequent association of other organisms, especially staphylococci, in the cultures, they felt that the diphtheroid bacillus was the one which most probably bore some specific relation to the disease, and were encouraged in this view by the development in a monkey, after injection of cultures, of a chronic progressive lymphadenitis, bearing some resemblance to Hodgkin's disease,⁵ and finally,⁶ by the production of progressive general glandular enlargement, with fever and leukocyto-

* Submitted for publication May 4, 1915.

* From the Medical Clinic of the Johns Hopkins Hospital.

1 Southard, E. E., and Canavan, M. M. *Jour. Med. Research*, 1915, **xxxi**, 339.

2 Bunting, C. H., and Yates, J. L. *THE ARCHIVES INT. MED.*, 1913, **xii**, 236.

3 Negri, E., and Mieremet, C. W. G. *Centralbl. f. Bacteriol.*, 1913, **lxviii**, 202 (original).

4 Fraenkel, E., and Much, H. *Ztschr. f. Hyg.*, 1910, **lxvii**, 159.

5 Bunting, C. H., and Yates, J. L. *Jour. Am. Med. Assn.*, 1913, **lxvi**, 1803.

6 Bunting, C. H., and Yates, J. L. *Jour. Am. Med. Assn.*, 1914, **lxvii**, 516.

sis, leading to the death of the animal. From the lesions, the diphtheroid organism was recovered in pure culture.

Billings and Rosenow⁷ were also successful in cultivating from Hodgkin's nodes diphtheroid bacilli similar to those described by the previous workers, and confirmed the frequent association of staphylococci with this organism. They reported favorable results from treatment with vaccines. Rosenow later⁸ published extensive cultural studies on tissues of various sorts. He isolated from the lymph nodes in acute and chronic arthritis, erythema nodosum, and Hodgkin's disease, a great many organisms, notably, streptococci, diphtheroid bacilli, *B. welchii*, and others. He noted, however, that none of these organisms was strictly limited to any one condition, and that often two or more were obtained from the same source. He was somewhat in doubt as to the interpretation of these findings, but inclined toward the position that in most cases the organisms were related causally to definite diseases.

Several less extensive studies have recently appeared, among which may be mentioned that of Lanford,⁹ who recovered diphtheroid organisms from the nodes in several cases of Hodgkin's disease, tuberculosis and lymphosarcoma, of Steele,¹⁰ who reports similar findings in a case of lymphatic leukemia, and, finally, the note by Rhea and Falconer,¹¹ on the cultivation of a pleomorphic diphtheroid bacillus from the nodes in a case of Hodgkin's disease.

The general result of these studies seemed to be the proof that viable bacteria are frequently present in lymph nodes *intra vitam* in conditions other than acute inflammation. The significance of the organisms, however, was by no means established. Thus, several possibilities immediately arose: (1) The glands might be filtering out saprophytic organisms which had accidentally become introduced into the body, (2) there might be a normal saprophytic flora of glands analogous to that of the skin, (3) the organisms might have persisted in the glands in more or less attenuated form after a previous acute invasion, (4) changes in the gland might have predisposed to invasion by certain organisms, and (5), specific organisms might be associated with specific histologic changes.

The following cultural studies were made, rather in the attempt to classify the bacteria obtained from glands, according to the above schema, than to investigate any particular diseases with the hope of finding an etiologic agent.

7 Billings, F., and Rosenow, E. C. Jour Am Med Assn, 1913, lx1, 2122

8 Rosenow, E. C. Jour Am Med Assn, 1914, lxiii, 903

9 Lanford, J. A. Am Jour of Trop Dis and Prev Med, 1914, ii, 191

10 Steele, A. E. Boston Med and Surg Jour, 1914, clxx, 123

11 Rhea, J., and Falconer, E. H. THE ARCHIVES INT MED, 1915, xv, 438

MATERIAL

It seemed advisable to draw material from as wide a range of conditions as possible. The glands which have been studied may be divided into two general groups. The first has been designated as the "normal" group, although it is recognized that no lymphatic gland is absolutely normal in the strict sense of the term, the nodes here included were, however, obtained from individuals either clinically well or suffering from a localized disease at a distant point, and the glands themselves were not enlarged and were essentially normal histologically. The second group consists of enlarged glands gathered from a considerable variety of diseased conditions.

TECHNIC

The material was obtained under the most careful aseptic precautions and, except in two cases, was planted within one hour of removal from the body. In no instance did over twelve hours elapse. A method of maceration was used essentially similar to that described by Rosenow,⁸ the steps in the process being briefly the following:

First, the material was washed through several changes of sterile salt solution, to get rid of blood and possible surface contaminations, it was then dipped in boiling salt solution, to further sterilize the surface, the length of immersion varying with the size of the piece of tissue. Next, it was ground up in a sterile box, suspended in a tube of sterile salt solution, and the resulting mixture added in varying amounts to the mediums. Blood-agar and Loeffler's serum, aerobic and anaerobic, and ascites-dextrose-agar shake tubes were used. The ascitic fluid was heated at 66 C for twenty-four hours, and stored in lots of 20 cc, each lot being controlled at the time of culture by several uninoculated tubes.

It seemed that a procedure of so many steps as this one might lead to frequent contaminations. A number of pieces of sterile potato were, therefore, run through in exactly the same way as the glands. It was found that the risk of contamination was about the same as that involved in the usual technic of transfer from tube to tube.

The cultures were all kept at least three weeks before being discarded. The number of colonies, their time of appearance, and general characteristics were noted, and subcultures made both aerobically and anaerobically on various mediums. In nearly all cases a portion of the gland was studied histologically, the interpretation being made in the pathologic department of the Johns Hopkins Hospital.

RESULTS

Thirty-two glands were studied, they may be divided as follows:

I "Normal" group (Seven cases)	
Glands from individuals clinically well	2
Glands from patients with arthritis, but not associated with an involved joint	4
Gland from periphery of a carcinomatous mass in neck — histologically normal	1

II Pathologic group (Twenty-five cases)

Hodgkin's disease	6
Carcinoma	6
Lymphosarcoma	3
Chronic infectious arthritis	3
Tuberculous adenitis	2
Subacute adenitis	2
Gaucher's disease	1
Acute leukemia	1
General glandular enlargement of obscure origin	1

The results have been classified from a number of points of view with reference to the simple presence or absence of organisms

1 Size—The glands varied roughly from 0.5 cm to 3 cm in diameter. Success in the cultivation of organisms bore no relation to size, the largest being sterile, and some of the smallest yielding as many as 1,000 colonies. The effect of Roentgen and radium therapy, of tuberculous softening, and of carcinomatous induration must be discounted in this consideration.

2 Duration of involvement—This was in most cases hard to determine with any degree of certainty, but varied certainly from three weeks to three years. No relation could be made out between the extent of invasion and the duration of the disease.

3 The special area or lesion drained—Only in isolated cases could this be correlated with the bacteriologic results.

4 The location of the gland bore no obvious relation to sterility, as may be seen from the following schema:

Location of Gland	Organisms Obtained in	Organisms Not Obtained in
Cervical (15 cases)	9	6
Inguinal (8 cases)	4	4
Axillary (4 cases)	4	0
Scapular (2 cases)	1	1
Epitrochlear (1 case)	1	0
Supraclavicular (2 cases)	2	0

5 The diagnosis—In this series a larger number of positive cultures was obtained from the definitely diseased glands than from those approaching nearer the normal, the percentage for the two groups being practically reversed:

	Organisms Obtained in	Organisms Not Obtained in
Hodgkins's (6 cases)	5	1
Carcinoma (6 cases)	4	2
Lymphosarcoma (3 cases)	2	1
Chronic infectious arthritis (3 cases)	3	0
Tuberculous adenitis (2 cases)	1	1
Subacute adenitis (2 cases)	2	0
Gaucher's disease (1 case)	1	0
Acute leukemia (1 case)	0	1
General glandular enlargement (1 case)	1	0
	<hr/> 19 (76%)	<hr/> 6 (24%)
"Normal glands" (7 cases)	2 (29%)	5 (71%)

From this analysis little information is to be gained further than that about two-thirds of the nodes contained organisms, the larger percentage of positive cultures being from the outspokenly diseased glands. The characteristics of the organisms, however, seem to throw them into several distinct groups.

Group I—Organisms which are to be correlated with the saprophytes on the body surfaces.

These organisms are aerobic, they occurred quite frequently in glands of all sorts, usually in small numbers (less than ten colonies to the gland in all but one case), were avirulent for rabbits, guinea-pigs and mice, and gave no immunity reactions with the patients' serum. They were encountered eleven times in a variety of conditions, including Hodgkin's disease, lymphosarcoma, carcinoma, and in 'normal' glands. Typical white staphylococci were identified eight times, and a spore-bearing bacillus, a *sarcina lutea*, and a *pseudodiphtheria* bacillus, each once.

They occurred at times alone, but often with the organisms of Group II.

Group II—Under this heading will be described two types of organisms notable by their frequent occurrence in these cultures, by their presence often in large numbers, and in pure culture, and by a characteristic relation of growth to oxygen tension.

The first type is a short pleomorphic bacillus, which appeared in cultures in from two to twelve days. Growth developed only in "partial pressure" tubes of ascites-dextrose agar, and was limited to the lower portions of the tube, in no case approaching nearer than within 1 cm. of the surface. The original colonies appeared as minute grayish or flesh-colored dots, some having a triangular or pyramidal shape, and reaching a maximum size of from 1 to 2 mm. in diameter in from ten days to two weeks. The rate and level of growth of various strains has been quite constant, and attempts to obtain surface cultures, either aerobically or anaerobically, have all failed. One strain has now been frequently subcultured over a period of twelve months, without inducing any change in these characteristics. The organisms are gram-positive, nonacid-fast, and stain readily with the aniline dyes. The younger cultures show mainly slender, rather short rods, usually smaller than true diphtheria bacilli, some straight and some slightly curved. No polar bodies can be definitely demonstrated, although occasionally the ends appear slightly expanded. Variations are seen from this type to that of a short, stubby bacillus, usually in pairs, which becomes the predominating form in older cultures. No beaded, clubbed or bizarre forms have been seen. In smears, the organisms tend to group themselves somewhat like diphtheria bacilli.

They are nonmotile The older cultures have a characteristic pungent, sour odor'

Ten strains of this organism have been isolated from twenty-five abnormal glands, the distribution being the following

Diagnosis	Cases	No Colonies
Carcinoma	4	75, 25, 2, 2
Hodgkin's disease	2	1,000, 1
Lymphosarcoma	2	150, 1
Arthritis	2	300, 2

In four instances, another type of organism was isolated, which showed the same peculiarities of growth level as the bacillus described above The colonies appeared in ascites-agar tubes in from two to five days, sharply limited to the subaerobic level, as discrete white pin-point disks, which were composed of gram-positive cocci, about the size of the usual skin cocci, but differing from them in the early appearance of variations in size, which was always striking by the time the colonies were large enough to be fished In subcultures they selected the same level, and thus far, it has been impossible to grow them, either aerobically or anaerobically, on the surface of plain, glucose, ascites, or blood-agar, Loeffler's serum, in fluid mediums, or in simple dextrose-agar stabs

This organism was first isolated from a cervical gland, in a case of acute Hodgkin's disease, the total duration from onset to death being only six weeks The culture was made three weeks before death, and yielded the organism in pure culture, the colonies numbering about two hundred A left cervical gland from the patient in a second case of typical Hodgkin's disease of about six months' duration yielded seven colonies of this coccus, with three colonies of a spore-bearing bacillus A gland removed later from the other side showed the coccus in pure culture In these two cases, then, the possibility arises of some special conditions favoring the invasion by this organism

Finally, in a case of lymphosarcoma, it was recovered from a cervical gland, together with the "diphtheroid" bacillus described above

Whereas the organisms included under the first group are obviously saprophytic and accidental, the significance of these two types does not seem so clear Their presence in glands, often in pure culture and in large numbers, their constant peculiarities with regard to oxygen tension, raised the question as to whether they might bear more than an accidental relation to the conditions in which they were found That they were not the specific cause of any one disease seemed established at the start by their occurrence in such a wide variety of conditions

The virulence of all fourteen strains was tried out on mice, guinea-pigs and rabbits The growth from two well-grown agar tubes was selected as the dose for a rabbit, one-half this amount for a guinea-pig

and one-fourth for a mouse. It seemed that these quantities were sufficient to test susceptibility, whereas, larger doses might produce non-specific effects. The inoculations were made intravenously, intraperitoneally, and subcutaneously. No specific lesions or general intoxications developed, the animals were, apparently, quite unaffected. It was noted that, after the subcutaneous injection, not even a local infiltration developed, there seemed to be no irritation or reaction. In two of the guinea-pigs, small temporary enlargement of the inguinal glands appeared after about a week, and then gradually subsided. The organisms could not be recovered from these glands. A monkey received repeated injections, into the axillary tissues, of large amounts of one of the "diphtheroid" strains, a temporary regional adenitis followed, the animal at no time seemed ill, and is now well after an interval of eight months.

In most of the cases, agglutination and complement-fixation tests were made with the patients' serums. The results were negative except with two of the anaerobic coccus strains, which fixed complement strongly with the serum of the patient in the case of Hodgkin's disease, from which one of them was isolated. Such a reaction is, perhaps, of similar significance to positive fixations with colon bacilli, certain streptococci, and other avirulent organisms.

Finally, injections of autogenous vaccines were given in five cases—two of Hodgkin's and three of infectious arthritis—not so much as a therapeutic procedure as to observe the reactions which might be set up. At least three subcutaneous injections at intervals of from four days to a week were made in each case. No effect, beneficial or deleterious, was observed. It was striking here also that large doses—ten thousand million and more—produced not even a local reaction, there was no tenderness, redness or induration.

In summary, then, these organisms seem to be parasitic but non-pathogenic, possibly certain types of gland lesion furnish a soil suitable for invasion by them.

Group III—Herein are included several isolated observations. From the inguinal gland of a child with a generalized, not suppurative, adenitis of probable cervical origin, were cultivated countless colonies of a typical hemolytic streptococcus of high virulence for rabbits. A week later, at a time when the process was subsiding, an axillary gland yielded about one hundred colonies of a white staphylococcus, no streptococci being obtained. A cervical node from a child with Gaucher's disease, showing typical histologic changes, yielded thirty colonies of staphylococcus aureus. This infection probably originated from an otitis media. Finally, from a gland in an atypical case of chronic arthritis, with splenomegaly, general adenitis, and leukopenia,

there were grown countless colonies of a chromogenic (yellow), small gram-positive diplobacillus, nonvirulent for small animals, but agglutinating and fixing complement with the patient's serum. This organism was encountered only in this instance.

CONCLUSIONS

It is clear, even from this small series of gland cultures, that the findings vary in significance in different cases. In view of the variety of organisms found, it seems that extreme conservatism should be maintained in interpreting any one as the etiologic agent of a specific disease. The following conclusions may, perhaps, be drawn.

- 1 As indicated by previous work, organisms can frequently be cultivated *intra vitam* from lymphatic glands.

- 2 There is a higher proportion of successful cultures from definitely diseased glands than from those approaching a normal condition.

- 3 Saprophytic organisms identical with or closely allied to the surface flora of the body are frequently filtered out, or, perhaps, constitute a more or less permanent flora of lymph glands.

- 4 Organisms are frequently isolated which seem by their biologic characteristics to be suited to live in relatively avascular areas, and which may tend to invade diseased glands, although they are not limited to them.

- 5 None of the twenty-nine strains isolated in this series could be shown to be the cause of specific diseases.

STUDY OF A CASE OF PAROXYSMAL HEMOGLOBINURIA

SERUM REACTIONS UROBILIN AND HEMOGLOBIN EXCRETION¹

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The uncertain nature of the hemolytic reaction characteristic of paroxysmal hemoglobinuria presents a problem of continued interest. The majority of investigators are agreed that the theory originally put forward by Donath and Landsteiner¹ explains in a general way the mechanism by which a paroxysm is brought about. But concerning the number and character of the different factors involved and the physical conditions under which they act, there are almost as many opinions as there are writers.

The first part of the paper is a study of this reaction. The second part deals with the quantity of blood destroyed during an experimental exposure to cold and the rapidity of the consequent excretion of hemoglobin by the kidneys.

As the literature contains many clinical descriptions of this condition, only a short history will be given and enough of the physical findings to establish the diagnosis and corroborate the data given by other investigators.

History and Physical Findings—C. S. R., boy, aged 12, colored, entered South Medical Service of the Massachusetts General Hospital, Nov. 18, 1914. Father and mother, three sisters and three brothers well. His mother has had no miscarriages. No history of syphilis obtainable. The patient had "rheumatism" from the age of 6 months to 3 years. Ever since the age of 3 he has had frequent attacks of hematuria, which occurred only during the winter following exposure to cold. The attack is often accompanied by a chill and followed by fever and pain in the stomach, without subsequent weakness. The hematuria never lasts more than a day. For the past six months he has been gradually losing his eyesight, first of the right, later of the left eye.

Physical Examination—The boy is undersized and only fairly nourished. Intelligent. Forehead bulging. Interstitial keratitis of both eyes. Teeth suggestive of Hutchinsonian type. Scaphoid scapulae. No glandular enlargement. Spleen and liver just palpable. Both shins show a definite periostitis. There is an effusion into all the large joints. The elbows show a slight limitation of motion.

Blood Examination—Red cells, 4,512,000. White cells, 10,000. Hemoglobin, 81 per cent (Sahli). Differential count, neutrophils 82 per cent, basophils, 17 per cent, mast cells, 1 per cent. Red cells of normal appearance.

¹ Submitted for publication April 28, 1915.

² From the South Medical Department and the Pathological Laboratory of the Massachusetts General Hospital.

³ Donath and Landsteiner. *Ztschr. f. klin. Med.*, 1906, lxxiii, 173.

Platelet count, 345,000 Coagulation time (method of Lee and White,²) nine minutes — upper limit of normal Wassermann strongly positive Urine negative except for hemoglobin after paroxysms, never bile, blood, casts or albumin

PART I SERUM REACTIONS

In view of the suggestion of all those who have worked with the serums of patients suffering from paroxysmal hemoglobinuria, the blood removed for experimentation in this case was kept at a temperature of 37.5 C until ready to be chilled The same precaution was taken with all other serologic material and organic extracts For the sake of space and convenience certain symbols are used in our work

N H Sr	Normal human serum
Pt Sr	Patient's serum
Pt Ch Sr	Patient's serum which has been chilled with patient's red blood cells at 0 C for one-half hour, centrifuged at the same temperature and the clear serum withdrawn
Pt R B C	Patient's red blood cells
Pt W R B C	Patient's washed red blood cells
N W R B C	Normal washed red blood cells
S W R B C	Sheep's washed red blood cells
G-P Sr	Guinea-pig serum
R Ambo	Rabbit amboceptor
In H Sr Anti	Inactivated human serum anticomplementary
C	Complete hemolysis
Ac	Almost complete
Pr	Partial hemolysis
Tr	Trace
0	No hemolysis

The first experiment consisted of the quantitative demonstration of the autohemolysin and of the native complement, which varied slightly from day to day (Table 1)

TABLE 1—QUANTITATIVE DEMONSTRATION OF AUTOHEMOLYSIN AND OF NATIVE COMPLEMENT EXPERIMENT 1 A

P W R B C				Result After 30 Min at 0°, Followed by ½ Hour at 37.5° C
Pt	Sr	+ 10 % Susp		
cc		cc		
04		025		C
02				C
01				Ac
005				Pr
0025				Pr
00125				Tr

EXPERIMENT 1 B

Pt	In	Sr	+ Complement	+ Pt	W	R	B	C	Result After 30 Min at 0° Followed by ½ Hour at 37.5° C
cc			cc		cc				
02			02		025				C
02			01		025				C
02			005		025				C
02			0025		025				Pr
02			00125		025				Tr
02			000625		025				0

2 Lee and White Am Jour Med Sc, 1913, clxxii, 495

Experiment 1 A shows that 0.2 c.c. of patient's serum is just sufficient to completely hemolyze 0.25 c.c. of patient's washed red blood cells.

Experiment 1 B shows that the amount of native complement present in 0.2 c.c. of patient's serum is equal to 0.05 c.c. of guinea-pig serum.

It has been stated by many observers, Meyer and Emmerich,³ Donath and Landsteiner,⁴ Cook⁴ and others, that the hemolytic amboceptor unites with the patient's red blood cells at 0 C in the absence of complement, then if complement is added later and the test is incubated at 37.6 C, hemolysis results. We were unable to confirm this observation. We found that all the different elements must be present throughout the whole reaction, that is, at the low temperature as well as the subsequent incubation at 37.5 C, or hemolysis does not take place. This is shown by the experiments recorded in Table 2.

TABLE 2—EXPERIMENTS SHOWING THAT HEMOLYSIS DOES NOT OCCUR UNLESS ALL ELEMENTS ARE PRESENT

Pt	In	Sr	Pt W R B C + 10% Susp, c.c.	Result after 0° for ½ Hour, then Warmed to 37.5° C, and 0.05 c.c. Compl Added, and Incubated for 1 Hour
	0.4		0.25	0
	0.2		0.25	0
	0.1		0.25	0
	0.05		0.25	0
	0.025		0.25	0
	0.0125		0.25	0

After the complement was added to each of the tubes previously warmed to 37.5 C and kept at 37.5 C for one hour, no hemolysis took place. Each element in turn was left out with the same result. If the complement is added to the tubes before they are warmed up to blood heat, strong hemolysis occurs for the simple reason that the union of these elements takes place in a few minutes in the cold, not necessarily at 0 C. It is obvious that it will require several minutes after the tubes have been placed in the incubator at 37.5 C to raise the temperature from 0 to 37.5 C. Thus, we found that in our experiments all elements must be present at a temperature below 37.5 C in order that hemolysis might occur. This result agrees with the findings of Moss⁵ and Hoover and Stone.⁶

Again, it is asserted by other investigators, Widal, Abram and Brissaud,⁷ that there exists in the serum of patients suffering from

3 Meyer and Emmerich. *Deutsch Arch f klin Med*, 1909, xcvi, 287.

4 Cook. *Am Jour Med Sc*, 1912, cxliv, 203.

5 Moss. *Johns Hopkins Hosp Bull*, 1911, xxii, 229.

6 Hoover, C F, and Stone, C W. *Paroxysmal Hemoglobinuria, THE ARCHIVES INT MED*, 1908, ii, 392.

7 Widal, Abram and Brissaud. *Compt rend Soc de biol*, 1913, lxxv, 502.

paroxysmal hemoglobinuria an inhibitory substance which prevents the union of the hemolytic bodies with the patient's red blood cells at 37.5 C, but which is inactive at lower temperature, thus allowing this combination to take place. It occurred to us that if such an inhibiting substance were present in the serum and could be isolated, it should exert a restraining influence on other hemolytic systems if brought into the proper relations with them. A plan was devised for isolating this substance, if it existed, and using it against the sheep-rabbit hemolytic system. Conceding that this inhibiting element is active at blood temperature and inactive at lower temperatures, it should remain free in the centrifuged fluid if the hemolytic amboceptor is given a chance to unite with the patient's red blood cells in the cold. This we attempted to do in the following experiments.

Two c.c. of patient's serum plus 0.25 c.c. of patient's washed red blood cells 100 per cent suspension was chilled for one-half hour at 0 C, centrifuged at the same temperature and the clear supernatant fluid withdrawn. This fluid should now contain the hemolytic inhibiting bodies free in solution, and if used against the other hemolytic systems might reasonably be expected to prevent their union. We were fortunate enough to have the serum of a patient which at this time and many times previously contained a serologic substance occurring in a sufficient amount in 0.2 c.c. of serum to prohibit absolutely the hemolysis of sheep's washed red blood cells by sensitized rabbit's serum, and this was used as a control in the experiment given in Table 3. For the sake of convenience the control experiment will be given first.

TABLE 3—CONTROL EXPERIMENT

In H S	+ 5% Susp,	Result After Adding 1 Unit	Result
Anti	S W R B C	R Ambo and Incubating	A f t e r Adding 0.05
c c	c c	$\frac{1}{2}$ Hour at 37.5°	Compl and Incubating 1 Hour at 37.5 C
0.4	0.5	0	0
0.2	0.5	0	0
0.1	0.5	0	Sl
0.05	0.5	0	Pr
0.025	0.5	0	Str
0.0125	0.5	0	C

Before the complement was added, the tubes were incubated for one-half hour at 37.5 C. There was no hemolysis at the end of this time (which was to be expected). This merely demonstrates the absence of complement. After the complement was added and the tubes incubated for one hour, 0.2 c.c. of this so-called anticomplementary serum was sufficient to prevent completely the hemolysis in the sheep-rabbit system. Smaller amounts allowed some hemolysis to take place for the reason that the anticomplementary substance was present in very small amounts. The serum used as a control had no natural

sheep's red blood cell hemolysins, while the blood of the patient did contain such substances

The foregoing experiment was repeated, the supernatant fluid removed from the cold-warm experiment being used instead of the anticomplementary serum

TABLE 4—EXPERIMENT TO SHOW THE ABSENCE OF INHIBITORY BODIES

Pt	Ch	Sr	W S R B C	Result After Adding 1 Unit R Ambo and Incubating ½ Hour at 37.5°	Result After Adding 0.05 cc Compl, Incub 1 Hour at 37.5 C
	cc		+ 5% Susp		
			cc		
	0.4		0.5	0	C
	0.2		0.5	0	C
	0.1		0.5	0	C
	0.05		0.5	0	C
	0.025		0.5	0	C
	0.0125		0.5	0	C

The complete hemolysis in all the tubes at the end of an hour demonstrated that the supernatant fluid used possessed no inhibiting properties. This evidence was further supported by the fact that the patient's serum possessed a very strong natural hemolysis for sheep's washed red blood cells which was in no way affected by these supposedly inhibiting substances.

From these experiments we must conclude that if there is a restraining substance present in the serum of hemoglobinurics which prevents the uniting of the specific substances at body temperature, it does not act in the same way on other hemolytic systems, since it did not in the least prevent the complete hemolysis of sheep's washed red blood cells by sensitized rabbits serum. On the other hand, 0.2 cc of a serum containing a known inhibitory substance did absolutely prevent the hemolysis of sheep's washed red blood cells. Furthermore, such a restraining substance did not exist in the serum of the patient suffering from paroxysmal hemoglobinuria. The physical and chemical composition of the autohemolytic amboceptor was such that it would not unite with the patient's washed red blood cells except it first be subjected to cold.

PART II UROBILIN AND HEMOGLOBIN EXCRETION

It has been shown by several investigators (Wilbur and Addis,⁸ Eppinger and Charnas⁹ and by one of us¹⁰) that the quantity of urobilin in the stool may be taken as an index of blood destruction. Blood destruction is greatly increased in diseases which show an abnormal amount of hemolysis going on in the body, as pernicious anemia, congenital hemolytic jaundice, etc. Quantitative estimations for uro-

8 Wilbur, R. L., and Addis, Thomas. Urobilin. Its Clinical Significance, *THE ARCHIVES INT. MED.*, 1914, xiii, 235.

9 Eppinger and Charnas. *Arch. f. klin. Med.*, 1913, lxxxiii, 387.

10 Robertson, O. H. *THE ARCHIVES INT. MED.*, to be published.

bilin¹¹ were made on the stools of this patient with the expectation of demonstrating an increased output following each paroxysm. Much to our surprise, there was practically no change in the quantity of urobilin excreted during two weeks in which he was given three exposures to cold, all of which were followed by hemoglobinuria. The absence of any increase could be explained in only two ways: first, that the amount of blood hemolyzed at each exposure was comparatively small, and second, that the kidney threshold for hemoglobin was very low, thus permitting a rapid excretion of this substance.

In order to determine the quantity of free hemoglobin in the blood serum and urine, a colorimetric method with a standard solution of hemoglobin was used. The standard solution, that is, one containing a known quantity of hemoglobin, was made by adding 10 c c of fresh blood to 100 c c of tenth-normal hydrochloric acid, which changed the oxyhemoglobin completely into hematin hydrochlorate, a more stable colorimetric solution. It was then diluted up to 1,000 c c with distilled water, thus producing a color suitable to work with. Finally the solution was centrifugated clear. The amount of hemoglobin per cubic centimeter of solution was determined in the following way. Sahli's hemoglobinometer was originally made up by using the blood of one or several individuals whose hemoglobin was 17.2 per cent of the total blood weight. Thus a blood reading 100 per cent on the Sahli scale would have 17.2 gm of hemoglobin per hundred grams of blood. The patient from whom the blood for the standard was taken had a hemoglobin of 40 per cent, therefore each hundred c c would contain 40 per cent of 17.2, or 6.88 gm. Ten c c would contain 0.688 gm, and when diluted to 1,000 c c each cubic centimeter would contain 0.000688 gm of hemoglobin.

The experiment was carried out as follows. Both feet and half the lower legs were immersed in ice water for five minutes. After eight minutes, 10 c c of blood were withdrawn from an arm vein into 1 c c of 1 per cent sodium oxalate solution. The boy was urged to micturate every few minutes. After forty minutes he had a slight chill and passed a few drops of deeply blood-tinged urine. Ten c c more blood were then taken. The blood in each instance was kept at body temperature from the time it left the vein until the serum had been separated from the corpuscles by centrifugation. This precaution was observed in order to prevent further hemolysis due to cooling. The second specimen of serum was much more deeply tinged with hemoglobin than the first, which was accordingly discarded. Two hours after the exposure to cold, he passed 23 c c of purplish-black urine. During the next two and a half hours he was given three

11 The method used was that of Wilbur and Addis (Footnote 8)

glasses of water in order that all hemoglobin might be washed out of the bladder. At the end of this time he passed 100 c c more urine only slightly blood tinged. That this was the last specimen to show any hemoglobin was indicated by the fact that a clear urine giving a negative guaiac test was obtained at each later passage.

To the blood serum were added $3\frac{1}{2}$ times its volume of tenth-normal hydrochloric acid, which was quite sufficient to change all the oxyhemoglobin into hematin hydrochlorate. The mixture was next centrifugated to throw down any suspended material. It was then read against a 1:2,000 dilution of the standard solution. After the addition of a few drops of lead acetate to each of the two separate specimens of urine, they were filtered. In this way all organic matter except hemoglobin was removed. Then, in order to insure against any loss of hemoglobin, the precipitate was washed with tenth-normal hydrochloric acid in a quantity equal to three or four times the amount of urine, and these washings added to the urine just filtered. Each urine solution which was quite clear was then read against a dilution of the standard solution somewhere near its color.

It was found that each cubic centimeter of the boy's blood contained 0.000592 gm of hemoglobin, and this multiplied by his total blood volume, which was estimated at 1,507 c c, using 1:19 as the ratio of blood weight to body weight, gave a total amount of 0.862 gm. The first specimen of urine contained 0.79 gm, which represented the hemoglobin excreted in the first two hours. The second specimen contained 0.04 gm, representing that excreted during the next two and one-half hours. The sum of the two, 0.83 gm, gives the total quantity of hemoglobin excreted in four and one-half hours. Calculating it in per cent, we find that he excreted in the first two hours 91.7 per cent of the entire hemoglobin set free, and in four and one-half hours, 96.3 per cent.

It was also very simple to estimate just how much blood 0.862 gm of hemoglobin represented. His blood showed a hemoglobin of 81 per cent; using the Sahli scale again, 81 per cent of 17.2 equals 13.9, that is, each 100 c c of blood contains 13.9 gm of hemoglobin, 1 c c containing 0.139 gm, $0.862 - 0.139 = 6.3$ c c of blood hemolyzed.

This exceedingly rapid excretion of hemoglobin accounts for the low urobilin output by the fact that the liver is given very little opportunity to transform the circulating hemoglobin into bile, which is in turn broken down in the intestine into urobilin. Even if the hemoglobin had not been excreted so rapidly, it is questionable whether the relatively small amount of hemoglobin set free would have produced a noticeable change in the amount of urobilin in the stool.

The apparent marked hemoglobinuria can be explained in the same way, namely by the very low kidney threshold for hemoglobin and its prompt excretion. The small amount of blood destroyed by the short but intense experimental exposure demonstrates that he could stand a great deal of cold without danger to life.

We realize that this method had its sources of error, the chief one being that it was impossible to judge the exact time after the paroxysm when the concentration of hemoglobin in the blood serum would be at a maximum. The time chosen may have been a little late, and some of the hemoglobin may have been excreted already, but as far as we could tell, he had excreted only a very small amount. We did not feel justified in bleeding him oftener at this time.

SUMMARY

The patient was a congenital syphilitic with characteristic physical findings and a strongly positive Wassermann.

The patient suffered from paroxysmal hemoglobinuria with typical attacks following exposure to cold.

These attacks could be induced at any time.

The characteristic hemolysis occurred under proper conditions in the test.

It was shown by experiments that the patient's serum, red blood cells and complement must be present throughout the whole reaction, or hemolysis will not take place.

The failure of the hemolytic reaction to take place unless the elements are first chilled together is not due to an inhibiting substance which is active at blood temperature but inactive in the cold, as the sheep-rabbit system is in no way affected when brought into proper relation with this system. The failure is probably due to the peculiar make-up of the hemolytic amboceptor.

The hematuria following a moderately severe experimental exposure to cold resulted from the destruction of only approximately 63 c c of blood.

Over 90 per cent of the hemoglobin set free was excreted in the urine within two hours, and 96 per cent in four and one-half hours.

The very rapid excretion of hemoglobin by the kidneys probably explains the absence of any increased amount of urobilin in the stools.

A STUDY OF RESPIRATION AND CIRCULATION IN PICROTOXIN CONVULSIONS

THE POSSIBLE BEARING OF THIS STUDY ON THE THEORIES OF PATHO-
GENESIS OF EPILEPTIC CONVULSIONS ¹

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The convulsion is the most prominent symptom of epilepsy. It is this symptom which has lent itself most extensively to the study of the pathogenesis of this disorder. There are many phenomena associated with convulsions which have received but scant attention. Chief among these are the circulatory and respiratory disturbances.

In *A Study of Respiration and Circulation in Epilepsy*¹ one of us found that preceding the convulsion in a case of *petit mal*, admirably suited for continuous respiratory and circulatory tracings, a constant series of events occurred (Fig 1).

A preliminary rise in blood pressure was noticed twenty-six to sixty seconds before the convulsion, when the rise took place over thirty seconds before a convulsion the blood pressure usually fell again slightly. Immediately preceding the convulsion by from nine to twelve seconds there was a sudden marked drop in blood pressure, which remained relatively low during the time occupied by the *petit mal* attacks.

Two seconds later the aura occurred. A period of apnea which preceded the convulsion or its equivalent then followed in from four to nine seconds.

From the facts that respiratory and circulatory disturbances preceded the convulsion or equivalents, the conclusion was reached, that in some cases of *petit mal*, the site of discharge is in the medulla and pons, and furthermore that the medulla and pons participate in the discharge in all cases of epilepsy whether this discharge originates there or not.

If convulsions which are caused by a discharge in the medulla and pons are accompanied by a train of circulatory and respiratory symptoms, it would seem likely that these symptoms should be present in a convulsion artificially produced by a medullary convulsant.

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¹ Pollock, Lewis J, and Treadway, W L. A Study of Respiration and Circulation in Epilepsy, *THE ARCHIVES INT MED*, 1913, xii, 445.

In this paper we wish to describe the circulatory and respiratory changes accompanying the convulsions produced by the administration of picrotoxin

Picrotoxin is the active principle of *Cocculus Indicus*, or fish berry. It is a medullary convulsant (Roeber²). The data tending to uphold this contention will be reviewed briefly below.

Its action along with coriamyrtin, is analogous to toxiresin and digitaliresin (Perrier³).

The description of the action of picrotoxin, will be limited to the convulsions, and its effects on the autonomic nervous system.

The convulsion resulting from the administration of picrotoxin has been recognized as being very similar to that observed in epilepsy, by many workers. It will be but briefly described. You may refer to a classical description by J. Crichton Browne⁴.

Following an injection of picrotoxin in a dose sufficient to produce convulsions without causing death (2 c c of 4 per cent alcoholic solution), the animal after a period of time, in which vomiting and salor-rhea may be noted, becomes quiet, sits in one place, and does not respond to calls. Then follows a period of unrest and apparent apprehension. The animal begins to tremble in fore or hind legs, or both, and lies on his side, at times trying to stand erect. Light twitches of face and neck muscles occur becoming stronger and stronger, the head is drawn backwards on the neck. Then immediately there follows a generalized clonic convulsion with clonic champing of the jaws, closing of the eyelids, marked frothing at the mouth, and involuntary urination. During the convulsion the pupils are dilated. The clonic convulsive movements imperceptibly change to running movements of the fore and hind legs, become slower and slower, and finally cease. The animal now remains quiet, lying on his side, and after some effort regains the erect position. After a period of time, varying with the size of the dose, another convulsion occurs.

It is generally admitted by pharmacologists that picrotoxin is a medullary convulsant. Adverse contentions, however (Bechterew,⁵ Browne⁴), have not been replied to adequately.

In the pharmacologic sense, convulsions are not clearly defined. They include many spasmodic movements, tremors, twitchings, and tetanic contractions. The pharmacologists have ignored, to a great extent, the work of other-departments in pathologic physiology in the

2 Roeber. Physiologische Wirkungen des Pikrotoxins, Arch f Anat u Physiol, 1869, p 38

3 Perrier. Toxiresin, etc, Arch f exper Path u Pharmacol, 1875, iv

4 Browne, J. Crichton. Brit Med Jour, 1875

5 Bechterew. Functionen der Nervencentra, 1908, vi, 187

study of convulsions The difficulty in correlating pharmacologic data with that obtained by neurologists and physiologists can therefore readily be seen

On the other hand, the neurologists who have attempted to prove that the medulla and pons are not directly concerned in convulsions, have not taken pharmacologic data into consideration The results of both must be considered in reaching a correct conclusion

Roeber² and Grunwald,⁶ working with picrotoxin, Albertoni⁷ with cinchonidin and camphor, and Perrier³ with toxiresin, digitaliresin, picrotoxin and coriamyrtin, are the principal workers who have attempted to prove that these various agents are medullary convulsants

Roeber was able to obtain convulsions with picrotoxin after removal of the cerebrum above the medulla He contended that picrotoxin is a medullary convulsant

Since the experiments of Perrier are very clearly given we will review those tending to show that the group of toxins above mentioned are medullary convulsants

From the fact that these substances cause convulsions he concluded that they act on the central nervous system On what part of the nervous system they act his further experiments show After removal of the hemispheres above the optic thalamus in frogs, convulsions occur following the administration of the poison After destruction of the thalamus and removal of the hemispheres, convulsions still occur When the medulla is separated from the spinal cord but two twitches of the head muscles occurred The rest of the body remained at rest After cutting through the spinal cord above the lumbar region convulsions occurred in the fore part of the animal only After section of the right ischiatic nerve the right leg did not participate in the otherwise general convulsion After the destruction of the medulla the animal quickly became comatose with no convulsion whatever

He therefore concludes that these substances in causing convulsions act on the central nervous system situated in the medulla oblongata

J Crichton Browne⁴ in a purely theoretic manner combats this idea as follows

Because the thumb and index finger may be moved by galvanic stimulation of the median nerve we do not argue that the movements of these parts are not ordinarily controlled by volition, and so because clonic spasms may occur in rabbits by irritation of the medulla after all other parts above the center have been cut off from it, we cannot argue that such clonic spasms may not proceed from the cerebrum when it remains intact

⁶ Grunwald Zur Kenntnis des Picrotoxins, etc, Arch f exper Path u Pharmacol, 1909, ix, 249

⁷ Albertoni Arch f exper Path u Pharmacol, 1882, xv, 258

It seems to us that Browne's objection is not applicable at all, for if, in experimental animals, the medulla after stimulation by picrotoxin acted only as a collection of fibers whose function is the conduction of impulses, then similar results would be obtained after section below the medulla, for these same fibers are found in the spinal cord. By this very objection Browne admits that the medulla at least shares with the cerebrum and ganglia a peculiar ability to be stimulated by picrotoxin which is not possessed by the spinal cord. If the medulla alone after stimulation by a drug causes convulsions in no wise different from those which are caused by stimulation of the cerebrum and medulla it is reasonable to assume that the convulsions may originate in the medulla. We must, however, admit that it is experimentally impossible to disprove entirely Browne's theoretic objection because it would necessitate the removal of the medulla and the substitution of some tracts leading from the cerebrum to the cord.

Bechterew⁵ has asserted that in his laboratory, after the removal of the hemispheres, clonic convulsions are not caused by the administration of cinchonidin and absinthe, while tonic convulsions occur.

Albertoni⁷ in the most careful work recorded found that in dogs after full operative recovery from half section below the optic thalamus with ensuing hemiplegia, cinchonidin produced a generalized bilateral convulsion. He further found that after full operative recovery from ablation of the motor cortex, similar generalized convulsions result from the administration of cinchonidin. He states that under these circumstances the convulsions are slightly diminished when camphor is the drug employed.

Grunwald⁶ observed typical picrotoxin convulsions in a decerebrated cat and dog.

We have found in two experiments on dogs, to be more fully described later, that in one after a section below the optic thalamus with a cautery knife and in the other after removal of the cerebral hemispheres and optic thalamus, picrotoxin caused convulsions differing in no wise from those occurring in animals with an intact central nervous system.

We are therefore convinced that there are drugs which are medullary convulsants and that picrotoxin is one of them.

In a work, the significance of which we will emphasize later, Grunwald⁶ studied the action of picrotoxin on the autonomic nervous system. He remarked that a review of the literature shows that aside from the production of convulsions and injury to the heart muscle, picrotoxin causes contraction of the pupils (Falck, Roeber, Luchsinger, Perrier, quoted by Grunwald), salivation (Falck, Roeber, Luchsinger, Gottlieb, also quoted by Grunwald), slow pulse (Roeber, Per-

rier, Gottlieb), urinary bladder contraction (Talek, Gottlieb), and erections (Luchsinger). All these disturbances may be attributed to the autonomic nervous system. In his experiments he verified these findings and demonstrated the central action of this poison as follows. After cutting the bladder nerves "no contractions occurred from the administration of picrotoxin."

In a decerebrated cat, poisoned with picrotoxin and showing a vagus pulse, salivation and bladder contractions, these three respective symptoms disappeared on section of the vagus, chorda and pelvic nerves; furthermore these symptoms did not again manifest themselves following a second dose of picrotoxin. After section of the right chorda, and the administration of picrotoxin, there was profuse secretion from the left salivary duct but none from the right. From these experiments he concluded that picrotoxin is a poison acting on the central autonomic nervous system.

We shall now revert to our supposition, that, if the respiratory and circulatory changes associated with a *petit mal* attack are due to a discharge in the medulla then we should find similar respiratory and circulatory changes associated with picrotoxin convulsions.

We shall not burden this paper with lengthy protocols. The experiments were conducted on dogs approximately of the same weight. Ether anesthesia through a tracheotomy tube was employed. The blood pressure was registered by means of a cannula inserted into the carotid artery and connected with a mercury manometer. The respiration was registered from the tracheotomy tube with a Marey tambour attachment. The time of injection of the drug and the beginning of the convulsion was recorded by means of a Du Bois Raymond key and electromagnet. A metronomic time marker was employed. The records were made upon a Stodding kymograph. The picrotoxin was administered as a 4 per cent solution either intravenously or subcutaneously. The action of the drug is much more rapid and severe when injected intravenously. Of a large number of records of convulsions observed in nine animals, twenty-three have been selected as suitable for study.

The data may be divided into general changes in blood pressure and respiration and the changes associated with convulsions. The general changes will be briefly dealt with. The blood pressure is raised after the administration of picrotoxin. Contrary to the findings of Grunwald we found that in a decerebrated animal the blood pressure did show a rise. A vagus pulse was observed in all cases. Picrotoxin acts as a respiratory stimulant.

With reference to the changes in blood pressure and respiration associated with convulsions, the material may be divided into four groups.

A Twelve convulsions in three animals following moderate doses of picrotoxin

B Two severe convulsions in two animals following large intravenous doses of picrotoxin

C Seven moderate convulsions occurring in one animal following a very severe convulsion as the result of a large intravenous dose of picrotoxin

D One convulsion in a decerebrated animal

In Group *A* which we term the typical reaction, we found that the convulsion started with twitching of the muscles, and respiratory irregularity, that preceding these symptoms by from three to ten, usually three to eight seconds, there was a fall in blood pressure which lasted until apnea had occurred. Apnea was concomitant with the severe clonic convulsion and did not precede it.

When respiration continued but was irregular during the convulsion, the blood pressure fell before the convulsion, and commenced to rise about five respirations after the severe clonic convulsion with its accompanying irregular respirations commenced.

In one tracing of Group *B* it was found that the blood pressure rose slightly with the convulsion and was associated with a few muscular twitchings and irregular respirations. A drop in the blood pressure and more marked twitching then occurred, followed by a period of apnea and severe clonic convulsions. The blood pressure continued to fall until almost the end of the period of apnea and then rose again.

In the other tracing of this group no period of apnea was present, and the blood pressure commenced to rise very shortly after the severe clonic convulsions began, having fallen before the convulsion began. It is to be noted that the first tracing of Group *B* is from the same animal that gave the seven tracings in Group *C*.

In Group *C* blood pressure began to fall during the period of apnea and rose during the period of respiration. The convulsion preceded the drop in blood pressure (Fig. 3).

In Group *D* a decerebrated dog, after an injection of picrotoxin developed tetanic convulsive movements, then irregular clonic convulsive movements, and, after a period of quietude a typical tonic-clonic picrotoxin convulsion which ended in running movements. Concomitant with this convulsion there occurred a drop in blood pressure and an increase in the respirations which had been very slow and irregular following the decerebration.

There were no Traube-Hering waves present in any of the tracings. The pulse was slightly increased in rapidity during all convulsions except such as occurred tumultuously where a vagus pulse persisted.

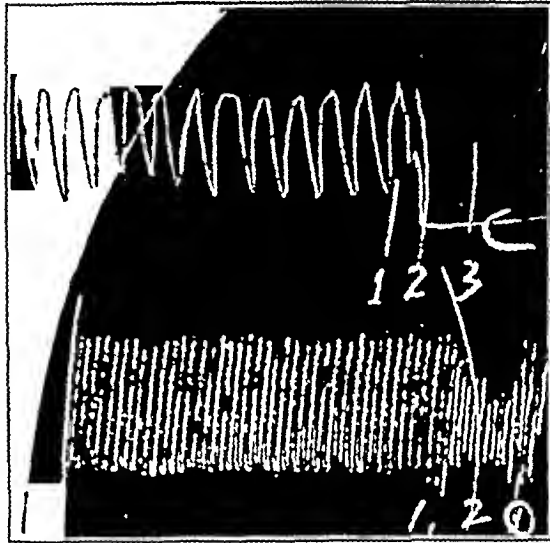


Fig 1—1, drop in blood pressure, 2, beginning of apnea, 3, convulsion

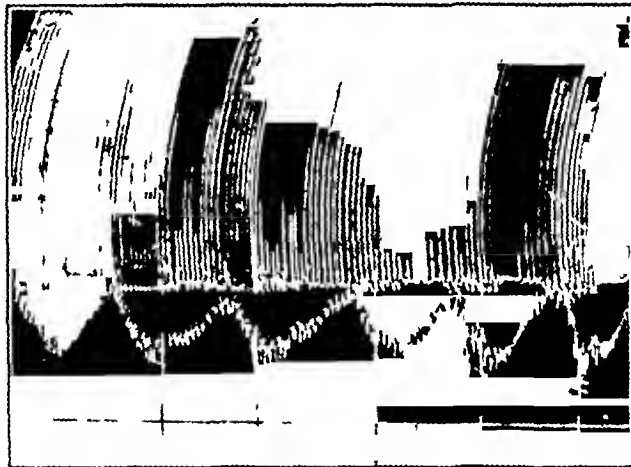


Fig 2—Convulsion preceded by drop in blood pressure

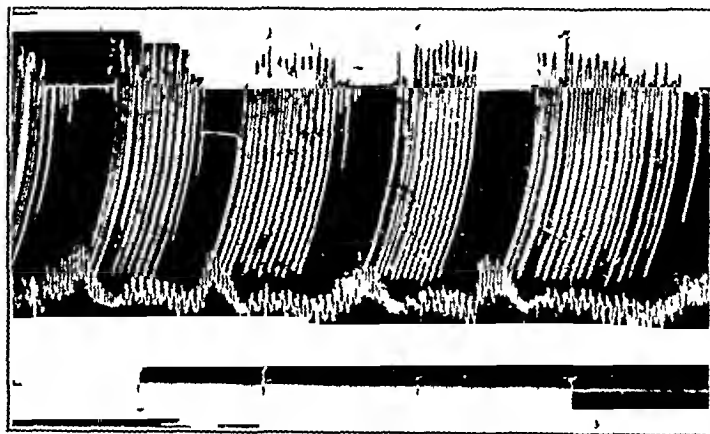


Fig 3—Convulsion followed by a period of apnea, during which the blood pressure fell

From the above facts it may be deduced that the period of apnea does not bear any definite time relation to the drop in blood pressure. In one series the blood pressure began to fall, and in another to rise at the beginning of apnea. When apnea was replaced by shallow regular respirations the blood pressure showed the same change. We also observed that the degree of blood pressure change is not influenced by the length of apnea, or the degree of respiratory irregularity. The period of apnea when present usually begins with the severe clonic convulsion. The changes in blood pressure, while concomitant with the convulsion, bear no definite time relation to it, neither can they be said to be the cause of the convulsion.

There now remains the interesting observation above noted, that in one series of convulsions the blood pressure rose with the beginning of apnea and fell in another series. In the first the blood pressure fell before the convulsion, in the other the convulsion preceded or was synchronous with the fall. This disparity affords an opportunity for certain definite conclusions. There are but few possible explanations of the cause of the diversity of changes in the blood pressure. The periodic rise and fall of blood pressure may be independent of either the respiratory changes or convulsions. In one series the blood pressure changes are those which regularly precede and accompany the convulsions. In the other series for some reason the blood pressure change may be due only to the period of apnea which results in such a fall of blood pressure as is found in the beginning of the so-called convulsions caused by strychnin, or the fall may be dependent on some change consequent to the convulsion.

In any event one conclusion can be reached. The periodic change in blood pressure is not due alone to either the convulsion or the period of apnea. It occurs in most cases as part of the manifestation of microtoxin poisoning, and although bearing no time or causal relation to the convulsion, nevertheless occurs about the same time.

The period of apnea can not be so easily explained. It might be the result of the participation of the respiratory muscles in the generalized convulsion. It might be due to the cerebral anemia resulting from the discrepancy of balance between a relatively low general blood pressure and a high intracranial tension (Cushing, Eyster, Pollock). Or it may be due to apnea, or depression of the respiratory center. Further work must be done to determine the cause.

We must here allude to the statement of Grunwald that the respiratory embarrassment is responsible for the rise in blood pressure in microtoxin poisoning. While it is true that by the use of artificial respiration he was able to prevent the rise it is true only with regard to the general blood pressure and it is not referable to the changes

about a convulsion. It is remarkable that although the blood pressure changes have been studied extensively in many toxic states, that even in strychnin convulsions the separate phases of blood pressure change associated with a convulsion are not described.

It is generally stated that during a strychnin convulsion blood pressure rises, yet although it does so, suddenly, with the first hard tetanic contraction it drops during the entire period of tetanic apnea and then rises to a great height. This same inaccuracy of observation we have already pointed out in our work on the circulatory and respiratory changes in epilepsy.

It may finally be said that although apnea and definite blood pressure changes occur along with the convulsion caused by picrotoxin, they do not bear the same constant relation to the convulsion as is found in *petit mal* states in man. Yet the independent variation in blood pressure occurring about the time of a convulsion is another proof of the medullary action of picrotoxin, which conclusion has been heretofore supported by its causing medullary convulsions and its action on the central autonomic system. The convulsion of idiopathic epilepsy is made up of a train of symptoms, the motor movements being but one of these.

Respiratory and circulatory changes, salivation, often involuntary urination, at times defecation and perhaps pupillary and thermic changes are as much a part of an idiopathic epileptic convulsion as are the motor disturbances.

Although artificially produced cortical fits may simulate imperfectly some of the motor disturbances of an idiopathic epileptic convulsion, it is only when an "after" generalized convulsion ensues as the result of a long continued cortical irritation, that the remaining symptoms such as salivation, etc., are present. The theory of the cortical origin of idiopathic epileptic convulsions fails, as pointed out by Hirt, to explain the presence of salivation, involuntary urination and respiratory change.

It would seem rather far fetched to search in the cerebral cortex for a center for the origin of these disturbances to place them alongside of Unverricht's area for the production of cessation of respiration and vascular change.

These symptoms may all be attributed to a disturbance of the central autonomic nervous system. They have been observed in picrotoxin poisoning and experimentally proved to be due to the action of this drug on the autonomic nervous system.

Toxic doses of picrotoxin cause not only convulsive motor disturbances but also such other symptoms as salivation, involuntary urination, etc., as are observed accompanying the convulsion of idio-

pathic epilepsy Although the circulatory and respiratory changes associated with the picrotoxin convulsion are not exactly similar to those found in idiopathic epileptic convulsions, yet the independent presence of blood pressure change associated with picrotoxin convulsions tends to show that these changes are part of the convulsion alike in picrotoxin and idiopathic epileptic convulsions

From the facts that there exist medullary convulsants and that their ensuing convulsions are associated with symptoms of disturbance of the autonomic nervous system similar to those found in idiopathic epileptic convulsions, and with circulatory disturbances analagous to those found in idiopathic epileptic convulsions, we conclude that we have further evidence that the site of discharge of the convulsion in some types of idiopathic epilepsy is in the medulla and pons The medulla and pons participate in the convulsion in all cases of epilepsy whether the site of discharge is here or not

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THE MORE RECENT DEVELOPMENTS IN THE STUDY OF ANAPHYLACTIC PHENOMENA

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I

It is a fundamental biological truth that the systematic treatment of an animal with a foreign protein, if this is administered by any route other than that of the alimentary canal, induces profound physiological changes. These changes are primarily recognizable by the appearance in the circulating blood of substances which superficially react with the injected protein. For convenience of discussion we speak of these reaction products as antibodies, and of the injected substances, which possess this power of inducing their formation, as antigens.

Antigens, then, are all substances which injected into the animal body, induce specific antibody formation. They form a large group in nature and are chemically proteins, indeed, we may say that all known proteins may act as antigens. Whether or not this term may also include lipid-protein combinations, lipoids or the higher protein derivatives is as yet uncertain and need not in the present connection concern us.

We may divide antigenic substances into two main classes. One of these comprises all of those substances of bacterial, animal or vegetable origin which, injected into the animal body, give rise to specific *neutralizing* or *antitoxic* properties in the blood of the injected animal. These are the bacterial exotoxins, the snake venoms, some powerful vegetable poisons and proteolytic and other enzymes of animals and plants. They are all substances which are powerfully active—some of them strongly toxic to the living animal, others true enzymes or ferments. Indeed all of them possess properties which at least suggest our placing them into the class of enzymes in general. The number of such substances known is limited. The reaction they call forth in the animal body seems aimed directly at the specific neutralization of their respective activities, and is so unique and different from that induced by other antigens that it would be convenient had we another term like “antitoxinogen” to set them apart by themselves.

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The other class of antigens comprises all proteins which are inactive, showing in themselves neither toxic nor enzyme-like properties. Introduced into the animal body parenterally, they call forth a response of a nature entirely unlike that of the antitoxins, and which as far as we can fathom its purpose seems aimed merely at the assimilation or the removal of the infected substance. For the cells of the animal cannot utilize the foreign protein as such, and thus it is only foreign proteins injected into an animal that act antigenically and no antibodies are formed when homologous material is injected.

This large group composed of all formed and unformed substances in nature in which a protein structure is involved, does not induce the formation of anything like the neutralizing antitoxins spoken of above. The antibodies appearing in animals treated with such substances have been spoken of as cytolytins or cytotoxins—precipitins—and in the case of formed antigens like bacteria or blood cells—agglutinins and opsonins. It is our opinion that all these various antibodies are identical in structure and significance. The probable identity of agglutinins and precipitins was suggested long ago by Paltauf, and the identity of precipitins with the antibodies which sensitize foreign proteins to the action of alexin or complement has been rendered more probable, we believe, by our own experiments. The terms agglutinin—lysin—precipitin and opsonin are all descriptive of effects produced when an antigen meets its specific antibody. These effects will differ according to the physical condition of the antigen. We believe that it is most likely, both from a study of the work of others and our own experiments aimed at this point directly, that the visible agglutination or precipitation are secondary effects incidental to the colloidal nature of the reacting bodies and to the quantitative proportions in which the reactions occur, the essential process being the union of antigen and antibody, by which the former is rendered amenable to the action of complement (alexin) or leukocyte as the case may be. It is not necessary, at any rate, to assume that functionally there is more than one variety of antibody, this one being the specific sensitizer. However this may be, the definite fact remains that injection of antigens of this second class into animals induces specific reaction bodies or antibodies in the plasma of the treated animal which can be shown to unite with the homologous antigen *in vitro*, and which probably do so in the body of the animal when the antigen is reinjected into a subject in which antibody formation has taken place.

We must not forget, however, that the observation of antibodies in the circulating blood is but one of the changes that have taken place in the treated animal. Much has been made of this phase of the problem because serum antibodies are readily studied *in vitro*, but

their origin of course must be sought in the body cell, in which the original and most profound changes must necessarily have taken place during such treatment, changes the nature of which are to a large extent still a mystery, but on which ultimately depend the important physiological difference between treated and untreated animals. For such changes—whether we refer to those immediately under discussion, namely, those of allergy or anaphylaxis, or whether we think of the so-called immunity remaining after attacks of many diseases—remain present long after the circulating antibodies have disappeared and must therefore be regarded as associated with profound alterations in the ultimate tissue unit, the body cell.

Pasteur's observation that animals systematically treated with sublethal doses of bacteria became specifically more resistant to subsequent infection, carries in it all the principles of the process of which we speak as "active immunization," and all the modifications and adaptations to special cases which we now employ are based on this simple truth. The successful transference of such increased powers of resistance to normal animals with the serum of the immunized individual, by Behring and his collaborators, gave us "passive immunization," and these two discoveries are the pillars on which all our complicated subsequent development of details has rested. Since with bacteria and their poisons the process implied the protection of the body against disease or death, we have, rather unfortunately, come to speak of these procedures as "immunization," although the reactions of the animal body to injections of bacteria, reactions on which incidentally the protection depends, are in principle identical with similar reactions resulting from the injection of entirely innocuous substances, such as egg albumin, blood serum or blood corpuscles. It is, therefore, misleading when we speak of the immunization of an animal to, for instance, sheep cells or horse serum. A physiological exchange takes place in such animals entirely analogous with that which occurs in those receiving bacterial protein, but the substances injected are in the former entirely harmless, and indeed, as we shall see, the animal, while entirely immune to large quantities at the first injection, may be severely injured or even killed by subsequent administrations of the same substance. Thus the animal most "immune" to horse serum is the one that has never received an injection of horse serum. It is necessary, therefore, to emancipate ourselves from the misleading elements in the habitual terminology so that we may avoid confusion in grasping underlying principles.

The essential feature common to all antigen injections, therefore, is that of specific antibody formation. That their production in the case of living or dead bacteria—harmful in themselves—protects the

animal from invasion and prevents development and multiplication of the organisms once admitted, though of the greatest practical importance, is purely incidental

It is not impossible that the physiological reaction indicated among other things by the circulating antibodies denotes a mechanism aimed at the more effective assimilation and elimination of the body-foreign antigens that have been injected, and this, in the case of the bacterial cell, which of course represents a foreign protein, has the effect of protection against invasion. This point of view of the significance of antibodies is the so-called theory of "parenteral digestion" of which we will have more to say directly. We must remember at any rate that in all cases in which, clinically or experimentally, we are confronted with the presence of foreign antigens in the blood and tissues, we are dealing with abnormal conditions in which the mechanism available under normal circumstances for the disposal of foreign proteins which may gain entrance accidentally in extremely minute quantities is under a strain and abnormally active. The extreme quantitative increase of the antibodies is alone sufficient testimony for this, and under the special conditions which we are about to discuss, the repeated introduction of such antigens into the body of an animal in which specific reaction bodies have been induced, whether these are freely circulating or still parts of the cells which produced them, may have illness or even death as a consequence. This is anaphylaxis.

To approach this subject logically without allowing secondary factors to divert our attention from the fundamental principles involved, we should not limit this term to any arbitrarily stated train of symptoms, nor should we attempt too rigidly to limit the definition of what we call anaphylaxis. Indeed, from the point of view of human pathology, it is of quite as much, if not of more, importance to study the effects of slow and slight injuries of this category, than it is to observe them only in the extreme and stormy manifestations of acute anaphylactic death. The former are the types of reactions occurring in the ordinary incidents of life. The latter are extreme results of experimental procedures and are for this reason of course more likely to reveal the underlying principles. But it would lead to false logic in our deductions were we to mistake a difference in degree for a difference in principle.

In the light of our present understanding, therefore, we should broadly define the term as the injury, acute or slow, severe or slight, which under manifold circumstances, may follow on the meeting of an antigen with its specific antibody within the animal body. When such injury fails to result in the case of the spontaneous entrance or the experimental injection of bacteria into an immunized subject it is

probably because the organisms are disposed of before the amount of foreign protein is sufficient to permit such a harmful reaction. What these circumstances are is the problem before us. In the case of innocuous foreign proteins such as blood serum or cells incapable of multiplication, it is doubtful whether immunity—that is, ability to escape harm on reinjection—ever exists. However, we do know that the animal may be nonsensitive, as on first injection when practically no specific antibodies are present, or it may be hypersusceptible, anaphylactic, or (the most comprehensive term) allergic.

II

We may discuss briefly the conditions under which so-called anaphylactic shock may be experimentally elicited in animals. Although of relatively recent development, in their details, the observations which underlie the phenomena took root in the early history of serum investigation. Morgenroth¹ speaks of an observation by Magendie as early as in 1839 in which he describes the sudden death of dogs when repeatedly injected with egg albumin. Fleñner reported similar deaths in rabies repeatedly injected with dog serum. Richet and Héricourt² in 1898 showed that toxic eel serum injected into dogs would kill at the second injection in far smaller doses than were necessary to kill at the first injection. Similar significance attaches to the work done by Portier and Richet on actinocongestine. Properly belonging in this group of phenomena are the early observations on hypersensitiveness to toxins in repeatedly injected animals made by Behring and his collaborators. The problem was brought into particular prominence by the observations of Arthus³ in 1903, who found that horse serum injected into rabbits at intervals of several days would eventually, in the later injections, give rise to severe infiltration and edema, and almost at the same time Theobald Smith noticed the great susceptibility to horse serum acquired by guinea-pigs that had been used for diphtheria antitoxin standardization. Independently and with great clearness of vision von Pirquet⁴ had made similar investigations on clinical material, and in his work on serum sickness appears to have grasped the fundamental significance of the phenomena with a thoroughness not shared by most of his contemporaries. The historical development of this subject and the experimental conditions under which hypersusceptibility may appear were the subject of a paper read before this society some years ago by two of the pioneer workers in this subject,

1 Morgenroth. Ehrlich *Gesammelte Arbeiten*, translation, Wiley & Son, New York, 1906, footnote, p. 332.

2 Richet and Héricourt. *Compt rend Soc de biol*, 1898, xv, 137.

3 Arthus. *Compt rend Soc de biol*, iv, 817.

4 Von Pirquet and Schick. *Die Serumkrankheit*, Wien, Deuticke, 1906.

Rosenau and Anderson⁵ The fundamental facts concerning the anaphylactic reaction were worked out almost immediately under the observations of Theobald Smith and Arthus by these workers and by Otto⁶ in Germany I may be permitted to summarize this early work and the fundamental principles of anaphylaxis very briefly in order that we may not spend our time in detailed consideration of facts entirely familiar to most of us

It is now certain that hypersusceptibility may be produced in human beings, in guinea-pigs, in rabbits, in dogs, in sheep and probably in all mammals, if we were to investigate them carefully

The condition may be produced by treatment with any of the substances known to us which have the property of antibody production, in other words, with all substances in nature of which we speak as antigens

The condition is like other antigen-antibody reactions, specific within the limits of specificity recognized for all such reactions It is certain that in so-called active sensitization, hypersusceptibility develops only after lapse of a definite interval, and this interval depends to a certain extent on the amount administered at the first injection

An animal once sensitized if not reinjected may remain sensitive for a long period, its sensitiveness will disappear immediately after recovery from a non-fatal reinjection or the animal may temporarily be desensitized by reinjection of the antigen at a period before hypersusceptibility has developed

Of the greatest theoretical importance furthermore is the fact that a normal animal may be rendered sensitive, passively, by the injection of blood serum from an actively sensitized animal, or by the blood serum of any animal which has been once or repeatedly injected with the antigen, and according to Doerr and Russ and others there is a definite parallelism between the capacity of a serum passively to sensitize an animal, and its contents in specific antibodies

There are many other facts which are of importance, but which for the present we will neglect, since these are the fundamental phenomena on which we may build our discussion We may also dismiss very briefly such earlier theories of anaphylaxis as those of Gay and Southard⁷ and Besredka,⁸ in which attempts were made to show that the substance which sensitizes is not identical with that which is responsible for the development of shock in the reinjected animal We may, indeed, disregard as premature theories, all those in which the anaphylactic reaction is removed from the sphere of true antigen-antibody reaction Indeed, von Pirquet and Rosenau and Anderson from the beginning regarded anaphylaxis as the result of the reaction between the reinjected antigen and the antibody formed in response to the first administration, and indeed, this is the essential premise of the still

5 Rosenau and Anderson Bull 29, U S P H S, 1906, Bull 30, 1906, Bull 36, 1907, Jour Med Research, 1906, xv, *ibid*, 1907, xvi, Jour Infect Dis, 1907, iv, *ibid*, 1908, v

6 Otto Das Theobald Smithsche Phaenomen, etc, von Leuthold Gedenkschrift, 1905, 1

7 Gay and Southard Jour Med Research, 1907, xvi

8 Besredka Bull de l'Inst Pasteur, 1908, vi, 826

earlier view of Vaughan. We may accept it at present, identifying the anaphylactic antigen with antigens in general, and the anaphylactic antibody with the protein antibody, not distinguishing for this purpose between agglutinins, precipitins, or cytolytins.

The symptoms which follow on the reaction of antigen into sensitive animals may show a wide range of variation according to the degree of sensitiveness and amounts injected. In acute anaphylaxis of guinea-pigs, which as you know has been the most thoroughly studied, there is a rapid and severe death which may not occupy more than a fraction of a minute or at most five to ten minutes. The animals repeatedly show restlessness, cough, piss, urine and feces develop severe dyspnea with infrequent respiration in which there seems to be almost complete immobilization of the chest wall and in which finally only shallow, irregular spasmodic efforts take place. This as Auer and Lewis have shown is due to tetanic contraction of the small bronchioles, with occlusion of the air passages, practically no air entering the lungs. As the dyspnea develops there may be at the same time spasmodic twitching of the limbs, retraction of the head and general convulsions.

When for some reason or other the reaction is not so severe the animal may show merely general signs of illness, puffing of the fur, twitching and restlessness with respiratory difficulty of varying degree, coughing, and excretion of urine and feces. In rabbits the symptoms are often less rapid in development but in general principles are similar, in rabbits there is more frequently in the moderate cases a gradual muscular weakness in which the animal lies flat on the ground unable to support itself on its legs, a condition which may proceed for long periods. Death is largely respiratory and the heart may continue to beat for a long time after respiration has completely stopped.

There is a sinking of blood pressure and a depression of temperature.

The coagulation time of the blood is lengthened, there is apparently a depression of the leukocytes, and according to a number of investigators, who have been recently confirmed by Behring, there is a disappearance of blood platelets and an increased flow of lymph.

Pathologically in an animal dead of anaphylaxis there may be petechial hemorrhages, according to Gay and Sonthard, in the heart muscle, pleura and intestinal wall and there may be fatty degeneration of the vascular endothelium. In guinea-pigs especially there is a marked emphysematous dilatation of the lungs which is very constant, although according to Doerr it is not absolutely characteristic of this condition. Apart from the anatomical changes following acute anaphylaxis, frequently repeated injections of small doses of horse serum or egg white in dogs, cats, rabbits and guinea-pigs have been shown by Longcope to produce cell injury in various organs, especially in the liver, myocardium and kidneys.

The sudden onset, the nature of the reaction in the animal and the pathological lesions seem to indicate that the injury as occurring in anaphylaxis is due to a poison. It appears, then, that an animal is sensitive to a protein at certain stages at which specific antibodies to the sensitizing protein have been formed, and that under special circumstances the meeting of antigen with antibody within the animal, results in a reaction in consequence of which the poisonous substance is liberated. This being the logical point of view on the basis of avail-

able knowledge, it was quite natural that many investigators were attracted by the theory of parenteral digestion⁹

III

It is one of the earliest premises of Pfeiffer's conception of bacteriolysis that the cell-dissolving action of immune serum liberates a preformed poisonous substance or endotoxin from the bacterial cell. It may be remembered that early in the history of such researches Pfeiffer and some of his pupils showed that an immune animal could be killed more quickly by large doses of dead bacteria than could a normal animal, an experiment from which the conclusion was drawn that the more rapid bacteriolysis in the immunized animal resulted in a more rapid liberation of the endocellular poisons. This point of view has been many times brought forward, and of recent years most clearly by Wolf-Eisner.

It is also a point of view represented by the theory of Nicolle, who similarly tried to explain anaphylaxis by the liberation of poisonous substances from the antigen through the action of the cytolytins or "albuminolytins."

As the investigation of antibody formation against foreign proteins of inherently harmless nature progressed, the belief gained strength that antibodies in facilitating the chemical disintegration of the injected foreign protein represented a sort of emergency apparatus for parenteral digestion and consequent assimilation. Throughout the development of Metchnikoff's ideas of immunity it is plain that he had tended toward such an interpretation, looking on the process of phagocytosis as a method of facilitating the removal of undissolved foreign substances from the tissues and blood, while the serum antibodies were conceived as more particularly concerned with the unformed foreign

9 The curious changes in the coagulation of the blood during the anaphylaxis have led to an interesting and important theoretical conception, namely, that the meeting of antigen and antibody may not, as otherwise believed, lead directly to the formation of a poison, but that in some way the results of such a union may influence the coagulation processes and that these alterations are the direct cause of shock. The first to give serious attention to such a train of reasoning was probably Nolf, and Doerr has recently called attention to the work of a number of investigators (recently confirmed by Moldevan) who observed that freshly defibrinated blood, i. e., blood in which the normal coagulation has been interrupted, may be toxic even when re injected into the same animal. The same is true of serum taken from rapidly defibrinated blood. There is at least a possibility, then, that the anaphylactic injury is the result of an alteration in the blood indirectly brought about by the union of antigen and antibody. However, the premises for such reasoning are still very vague, and moreover, any view which introduces the various elements which participate in blood coagulating processes can have no part in such manifestations as those observed on isolated and washed tissues, as in the experiments of Schultz and Dale.

proteins which in the accidents of ordinary life gained entrance. The most clear and thorough exposition of such a point is that which since 1907 has been carefully worked out by Vaughan, and to him belongs the credit for the development of many of the ideas underlying prevalent opinions on anaphylaxis. Vaughan, as you well know, subjected many different proteins, bacterial and others, to hydrolytic cleavage in absolute alcohol containing 2 per cent of hydroxyl.

The protein is covered in flasks with 25 to 30 times its weight of this alkaline alcohol and the mixture boiled at 78 C. for an hour or more. In this way he has succeeded in splitting off from a large number of different proteins the toxic fraction.

Since Professor Vaughan¹⁰ himself has but recently embodied his views in a concise treatise, it is quite unnecessary to go into it more than to review briefly his views. He believes that all true proteins contain a poisonous group which is practically the same in all of them. This poison can become free and active when proteins are submitted to various methods of decomposition. Protein sensitization, in other words, is due to the fact that there is developed after the first injection a specific proteolytic ferment, and this on second injection so acts on the reinjected antigen that the toxin fraction is set free and poisoning results. This, in brief, is Vaughan's point of view and is supported, first, by the fact that such poisons can be formed by his chemical methods from many different kinds of protein, and second, that these poisons, whatever the antigen from which they are derived, may produce symptoms which are in many ways identical with those characteristic of anaphylactic shock. Since, as Vaughan states, proteolysis consists in a gradual breaking up of the protein molecule into simpler and simpler groups, there is an increase of poison liberation up to a certain point in the process, but when it has proceeded beyond this the poison itself is decomposed and ceases to have toxic action. Vaughan believes that anaphylaxis in all its manifestations, whether acute or chronic, is merely an incident in parenteral protein digestion. In the course of this when the relation between circulating antigen and the specific enzyme is such that large amounts of the toxic fraction are suddenly liberated, acute shock follows.

It is hardly necessary to call attention to the attractiveness of such a theory, which so simply explains the apparently mysterious conditions prevailing in anaphylaxis, and there seemed to be very little doubt as to its correctness when Friedemann¹¹ some years later showed that the action of fresh unheated serum (i.e. alexin or complement) on sensitized red blood cells will produce a poison that, injected into

10 Vaughan. Protein Split Products, etc., Lea & Febiger, 1913.

11 Friedemann. Ztschr. f. Immunitätsforsch. u. exper. Therap., 1909, 11.

rabbits, gives rise to anaphylaxis-like shock. Following him Friedberger¹² succeeded in producing a similar poison by allowing fresh guinea-pig serum (i.e., complement) to act on both precipitates formed by the union of the serum with its antiserum and on sensitized and unsensitized bacteria. These investigations clearly suggested that the action of the alexin present in the circulating blood, on an antigen sensitized with its specific antibody, might produce protein cleavage in which there was liberated a toxic fraction similar to that produced by Vaughan with his chemical hydrolytic methods. It is but natural, therefore, that Friedberger, to whom the greatest credit in the more recent development of this point of view belongs, should assume that the poison liberated in this way is the toxic factor concerned in anaphylaxis, and name it "anaphylatoxin." For reasons which will appear directly, we think that a preferable term would be "proteotoxins."

The technic developed by Friedberger consists, in the case of dissolved proteins, in allowing the antiserum to act on the serum until a precipitate is formed, then subjecting this precipitate to the action of fresh guinea-pig serum or complement. After a variable number of hours, the length of time depending on secondary factors, which need not be discussed in describing the process, the centrifugation removes the precipitate, the supernatant guinea-pig serum is found to be strongly poisonous, and injected into guinea-pigs intravenously in quantities of from 2 to 4 c.c. produces symptoms typical of acute anaphylaxis. With bacteria his technic is similar. At first bacteria sensitized with inactive immune serum were subjected to the action of fresh guinea-pig complement for from one to two hours at 37 C. to as long as twelve to twenty-four hours at refrigerator temperature. At the end of this time the bacteria is removed by rapid centrifugation, and the supernatant fluid injected into guinea-pigs produces again typical symptoms of acute anaphylaxis.

The first interpretation applied to these experiments by Friedberger was an entirely natural one if we consider the general views held before this concerning bacteriolytic and bactericidal processes. He assumed that the complement acting on the sensitized bacteria or on the sensitized protein in the precipitate experiment (or later on the unsensitized bacteria), produced proteolytic changes in the course of which the toxic split product was formed. It seemed that the poison was pharmacologically the same whatever the antigen used, and experiments also seemed to show that the poison could be produced more rapidly from strongly sensitized than from unsensitized bacteria, and that an excess of sensitization or a too prolonged interaction resulted in nontoxic supernatant fluids, which was taken to indicate that the protein had been split beyond the toxic stage by too energetic hemolytic action.

¹² Friedberger. Berl. klin. Wchnschr., 1910, Nos. 32 and 42, Ztschr. f. Immunitätsforsch., 1910. iv

Here, then, we have a simple and apparently logical explanation of anaphylaxis, entirely in accord with Vaughan's views of parenteral digestion. An antigen is injected into an animal, specific antibodies and enzymes against it develop in the animal, re-injection of this antigen results in relatively rapid proteolysis in the course of which poisonous substances, the anaphylatoxins, are produced and anaphylaxis is the result. This hypothesis although very attractive does not entirely meet with the facts as they have been developed since Friedberger's first work. The premises on which it is based assume in the first place that the poison or "anaphylatoxin" is formed out of the matrix of the antigen, further, it is definitely assumed that in the production of the poison after the antigen and antibody have met, the complement or alexin plays an active part. Friedberger's hypothesis as stated by him, moreover, seems to assume that the entire process takes place intravascularly, a matter which we will discuss at considerable length in a short time. It is important to note also that Friedberger, with Nathan, was able to show that this anaphylatoxin production could take place within the animal body, that is, within the peritoneum of a guinea-pig into which bacteria had been injected.

The simplicity of Friedberger's explanation and the correctness of his experimental data soon persuaded many investigators that, in essence, his hypothesis probably contained the nucleus of the solution of this difficult problem. However, even his own early experiments aroused some misgivings concerning the matrix of the poisons produced, for he found that the poisons could be obtained as well when boiled antigen was used as when the fresh, unheated substances were employed, and the poisons were easily obtained from such organisms as the tubercle bacillus, which is extremely insoluble and unamenable to serum influence. It was also doubted whether one could truly assume the participation of this specific antibody or sensitizer in the production of Friedberger's poisons, since it soon developed that from bacteria, at least, the poison could be produced when the organisms were directly exposed to the action of fresh guinea-pig serum without the presence of any immune serum.

Experiments which soon threw a definite doubt on the assumption that the poisons were produced by a decomposition of the antigen were reported by Keysser and Wassermann¹³. These workers substituted insoluble substances like barium sulphate and kaolin for the antigen, that is, the precipitates or bacteria used in Friedberger's experiments. They found that if kaolin were treated with horse serum and then exposed to the action of guinea-pig serum or complement,

¹³ Keysser and Wassermann. *Folia serol*, 1911, vii, *Ztschr f Hyg u Infektionskrankh*, 1911, lxxviii.

poisons were produced identical in every respect to those produced by Friedberger's method. The conclusions they drew were that the poisons were produced, not by action of the complement on the antigen, but by its action on the horse serum absorbed by the kaolin. In other words, they transferred the matrix of the poison from the antigen to constituents in the serum itself, possibly the sensitizer or amboceptor. Bordet¹⁴ also was able to show that poisons similar to those of Friedberger could be produced by the action of fresh guinea-pig serum on agar, and recently Bordet has further shown that this is the case even when the agar has been by special methods deprived entirely of its nitrogenous components and represents simply a complex of carbohydrates. Agar-guinea-pig serum mixtures of this kind show an increase in total nonprotein nitrogen which would prove that the proteolytic action of the guinea-pig serum must have been active against its own proteins.

An interesting further development of this work has recently appeared in the experiments of Jobling and Peterson¹⁵. They showed that when bacteria are mixed with fresh active serum they adsorb the antienzymes normally present in blood. They have shown this experimentally and have proved that similar antienzyme removal can be accomplished by the addition of kaolin or agar, and by treatment with chloroform. Serums so treated become toxic, the actions of the poisons formed showing great similarity to that produced by Friedberger's anaphylatoxins. According to them, the poisons are formed because of the fact that antienzymes are adsorbed by the antigen, thus setting the normal ferments in the fresh serum free to act on their own serum protein.

It should be recalled that Friedemann, who was really the first one to show that the toxic substances could result from the interaction of fresh serum and sensitized antigens, although he succeeded only in doing this with red blood cells, suggested rather early that the success of such an experiment does not necessarily mean that the antigen furnishes the matrix entirely. He had studied the metabolism in anaphylactic poisoning and with Isaac has shown that the nitrogen output following reinjection in a sensitized animal is far in excess of that which could be derived solely from the injected antigen, and in this he has been confirmed by many other workers, notably by Vaughan.

It would seem to us that our present knowledge of this phase of anaphylactic investigation permits us only to conclude that wherever proteolytic changes take place these "proteotoxins" may be formed. That they can be produced from a protein antigen has been shown

14 Bordet. *Compt rend Soc de biol*, 1913, lxxiv, 877

15 Jobling and Peterson. *Jour Exper Med*, 1914, xix, No 5

beyond doubt by Vaughan and his collaborators for both formed and unformed antigens. Also this is evident from the experiments of many workers and has been confirmed in our own experience with poisons appearing during the autolysis of bacterial emulsions. On the other hand it is also clear that the antigen need not represent the matrix which furnishes the poison, and that in the reactions as they are generally performed both in the test tube and in the animal body, it is more than likely that if an antigen participates at all in furnishing the substratum for the poison, this is probably less important than that furnished by the animal's own proteins. However, this does not weaken the importance of the knowledge that the antigen-antibody reaction in the presence of normal serum and certain antigens in the presence of normal serum alone, induce a reaction in the course of which such poisons are formed. And the fact that they can be produced experimentally in the peritoneal cavity of a living guinea-pig renders their participation in such reactions in the animal body a likely assumption.

Our own work¹⁶ on these substances induces us to believe that proteotoxins so formed are identical with Bail's aggressins, a point to which we will later refer.

Granted that such a poison, call it "proteotoxin" or "anaphylatoxin" or "serotoxin," as Jobling and Peterson have called it, is formed, it is important of course to determine as closely as possible its nature. Apparently the poison is the same as far as we can determine by pharmacological action when produced by the chemical methods of Vaughan or by the biological methods of Friedberger and others. As obtained by Vaughan it is water-soluble with slightly acid reaction, is freely soluble in alcohol and mineral acids. It is not diffused readily and contains no carbohydrates. In its crude state it gives a biuret reaction, although this may mean simply that the poison has not been completely derived. The fact that the injection of Witte peptone into animals may give rise to symptoms very similar to anaphylaxis has been taken by many workers to signify that the anaphylactic intoxication is produced by a poison which is very similar to, or possibly identical with, the active constituents found in this peptone. After peptone injection in normal animals there is a lowering of blood pressure, a delay in the coagulation of blood and a development of subsequent tolerance, together with many clinical symptoms which emphasize this similarity. Biedl and Kraus, who have especially studied this condition in dogs, have felt emphatically that the anaphylactic poison is probably very similar to peptone. Recently Dale has suggested that B-imidezolyethylamin or histamin may be the active principle con-

16 Zinsser and Dwyer Jour. Exper. Med., 1914, xx, No. 6

cerned in anaphylactic shock. Intravenous injection of 0.5 mg. of this substance into large guinea-pigs results in typical respiratory difficulties, convulsions with death and distention of the lungs typical of anaphylactic shock. Treatment with atropin diminishes this action, just as Auer and Lewis found this to be the case in true anaphylaxis, and fall in blood pressure also occurs. It would seem then that substances representing cleavage products of native proteins of highly complex nature, the result of proteolytic cleavage not very far advanced, are probably concerned in the production of anaphylactic shock. The anaphylatoxins of Friedberger cannot of course be studied chemically by the methods to which Vaughan's poisons are amenable.

IV

A further problem which has arisen in connection with the conception of parenteral digestion is that which concerns the participation of complement or alexin in the cleavage process during which the anaphylactic noxious agent is liberated.

When bacteria or red blood cells are sensitized, that is, have been combined with their specific antibodies, we have believed that it is the complement, or active constituents of fresh blood, which then acts on this sensitized complex, either producing hemolysis in the case of sensitized red blood cells, or the bactericidal or bacteriolytic effect in the case of sensitized bacteria. It is also well known to you that this substance, which we call complement or alexin, but about the true nature of which we know nothing, is fixed or bound by dissolved proteins when they have combined, with or without the formation of precipitates by their antibodies. We have ourselves¹⁷ shown that such fixation of complement by precipitates (formed when an antigen and its precipitin have united) is bound in exactly the same way as this occurs in the case of sensitized red blood cells, that it is not a non-specific physical complement fixation such as that which occurs when complement is fixed by kaolin, yeast cells or other unsensitized emulsion. From this knowledge there has gradually grown the conception that the complement or alexin may be a necessary, active factor in the cleavage of the antigenic molecule. (This may or may not be so, we may say we think that we have no proof at present that the complement acts as a proteolytic enzyme, on the other hand it is more than likely that in some way it is connected with such cleavage processes.) At any rate, since we know that the anaphylactic reaction is the result of the union of an antigen with its antibody, and this together with our knowledge of complement fixation, naturally suggests that the complement may be directly concerned in the mechanism of anaphylaxis.

¹⁷ Zinsser Jour. Exper. Med., 1912, LV, No. 5, 1913, LVIII, 219

The first method of approaching this problem naturally was the examination of animals with regard to quantitative changes in the complement contents of the blood during anaphylactic shock. It was found by Sleswijk¹⁸ that animals actively sensitized and re injected showed a very definite diminution of complement. However under such conditions the diminution was neither rapid nor very extreme, facts since confirmed by Friedberger and Hartoch,¹⁹ who found the diminution very much greater in experiments with passive sensitization. In such cases there was a regular and considerable diminution, so that after shock four to eight times as much serum was necessary to produce the alevic effect as before shock. Friedberger even believed that there was a definite parallelism between the intensity of shock and the degree of complement diminution. The question immediately arises is the loss of complement, which we may now regard as a demonstrated fact, an incidental effect of shock or has it causal relationship to the development of shock? The latter seemed at first to be likely for a number of reasons. It was found, in the first place, that the addition of complement to the circulation of an animal during the anaphylactic experiment did not serve to prevent shock. Similar evidence seemed furnished by certain experiments on the complement of birds, by work of Loeffler²⁰ and by the observation of Hartoch,²¹ that but slight shock could be produced in guinea-pigs suffering from trypanosomiasis in which, as is well known, complement is greatly reduced. Loeffler also attempted to support this point of view by sensitizing guinea-pigs and then reducing their complement by the injection of sensitized beef blood intraperitoneally. Such animals showed diminution of reaction when re injected with the sensitized antigen. Loeffler's experiments are not conclusive, since the action of the sensitized blood cells in the peritoneum must surely have induced an intoxication not at all unlike that taking place in true anaphylaxis, and, as we have shown recently together with Dr Dwyer, such intoxications are followed by nonspecific tolerance to the anaphylactic poison.

However, another method of approaching this problem was attempted by Friedberger in his well-known salt experiment. It had been shown by a number of workers, among whom we may mention especially Nolf²² and Hektoen,²³ that complement is not bound by sensitized complexes in the presence of hypertonic salt solution. In fact, hypertonicity seems to inactivate complement, and indeed it is a method

18 Sleswijk. *Ztschr f Immunitätsforsch*, 1909, ii

19 Friedberger and Hartoch. *Ztschr f Immunitätsforsch*, 1909, iii

20 Loeffler. *Ztschr f Immunitätsforsch*, 1910, viii

21 Hartoch and Sircnskiy. *Ztschr f Immunitätsforsch*, 1910, vii

22 Nolf. *Ann de l'Inst Pasteur*, 1900, xiv

23 Hektoen and Rudiger. *Jour Infect Dis*, 1904, i

of many laboratories to preserve complement for considerable periods by adding hypertonic salt solution, in which condition it will last a considerable time and is easily reactivated on dilution to isotonicity with distilled water. Friedberger²⁴ injected concentrated salt solution into sensitized guinea-pigs just before reinjection. It is possible, as he found and as we have found since, to inject 0.3 c.c. or even more of saturated salt solution intravenously into guinea-pigs of about 200 grams weight without killing them. When sensitized guinea-pigs were injected in this way and immediately afterwards received a toxic antigen injection, shock was definitely diminished and death averted. This has been one of the strongest bulwarks of those who have believed in the participation of complement in serum anaphylaxis. And it was assumed that the mechanism of the salt experiment consisted in a prevention of complement action. Recently doubt has been thrown on this because Ritz²⁵ has shown that salt injection not only prevents anaphylactic shock but will prevent the toxic effects of Witte peptone and of the so-called "anaphylatoxins." Recently with Dr. Dwyer²⁶ we have carefully repeated this work and have found that when the dose is carefully adjusted there is no question about the fact that an immediately preceding injection of concentrated salt solution will prevent death or even symptoms in animals injected with proteotoxins. This tends very strongly to diminish the weight of Dr. Friedberger's interpretation of the salt experiment, it means either that the salt in diminishing anaphylactic shock does so by a mechanism not concerned with the prevention of complement, or else it signifies that the so-called proteotoxin itself is not a finished poison as it has been thought to be but must still be acted on by the active constituents of serum before it becomes active.

It is true, indeed, that heating serum to a temperature of 56 C renders it impotent to lead to proteotoxin production when added to antigen *in vitro* and that this same inactivation destroys the complementary effect on sensitized red cells or bacteria. This, after all, does not prove identity of the substances carrying these activities, but merely establishes an interesting parallelism.

We must not forget that the substance of which we speak as "alexin" or "complement" is not very well understood. We know little of its nature. It has been successfully shown that globulin participation will divide it into two parts, that it will spontaneously reactivate to a slight degree after heat inactivation, that its activity is influenced by concentration, and that it can be inactivated by shaking. We are

24 Friedberger and Hartoch. *Ztschr. f. Immunitätsforsch.*, 1909, III

25 Ritz, cited by Doerr. Footnote 29

26 Zinsser and Dwyer. To be published

aware of the fact that we are here, possibly, dealing not with a single substance, but with one of the effects of a complex serum constituent. As to its relation to anaphylaxis we can only say that the diminution of complement during anaphylaxis is perfectly definite. However, we cannot claim with certainty, in spite of the evidence so far advanced, that it plays an active part in the production of anaphylactic shock.

A

The fact that the hypersusceptible condition can be transferred from a treated to a perfectly normal animal with the blood serum of the former, was in itself one of the first strong arguments in favor of the antigen-antibody conception of anaphylaxis. And this point of view was still more clearly defined when Doerr and Russ²⁷ subsequently showed that the power of a serum to convey hypersusceptibility was directly proportionate to its contents of specific antibodies. A serum which was strongly precipitating for the antigen would passively sensitize in quantities far smaller than those necessary for the same purpose in the case of a weakly precipitating serum. The principle that anaphylaxis depended directly on the meeting of the antigen with its specific antibody has never been seriously questioned since this time. However, from the very beginning of experimentation on passive sensitization it has seemed unlikely that the acute reaction, as seen especially in guinea-pigs, could be attributed entirely to the meeting of these two elements in the blood stream. It was observed by Nicolle, Otto, Friedemann, Gay and Southard and by many others since then, that sharp reactions can be produced with regularity only when a distinct interval was allowed to elapse between the administration of the sensitizing serum and the injection of the antigen. When the two are injected together, mixed, or simultaneously, symptoms may be and usually are entirely absent, whereas severe and unfailing shock results when the antigen injection is deferred from twelve to twenty-four hours after that of the sensitizing serum. According to Doerr and Russ the interval may be shortened to four hours, but if lessened beyond this, the reaction may fail to appear, or if present at all is weak and indistinct.

This observation alone would tend to convince us that mere contact within the blood stream of antigen cannot account for the entire train of phenomena and suggests that the characteristic anaphylactic reaction takes place only after the injected antibody has become attached to the body cells in the same manner.

The idea in itself is not new. Wassermann had first suggested it in an attempt to explain the peculiar hypersusceptibility to toxin possessed

27 Doerr and Russ. *Ztschr. f. Immunitätsforsch.*, 1909, iii.

by some of Behring's toxin-immunized animals. He assumed that in such animals the formation of antitoxins may indeed have been stimulated, but that much of it might still be attached to the generating cells themselves, thereby rendering these proportionately more vulnerable to the injected toxin.

Such a conception of "sessile receptors" was applied by Friedberger²⁸ to anaphylaxis in his first attempts to formulate an hypothesis. He assumed that at the first or sensitizing injection the production of antibodies (precipitins) was stimulated. These, however, were not produced in great quantity and were not discharged into the circulation, possibly owing to the small single dose given for sensitization. They were present at the end of the anaphylactic incubation time as sessile receptors or sessile antibodies (precipitins). On the second injection a reaction occurred between the injection antigen and these sessile precipitins and the cell was injured because the reaction occurred on its substance, a reaction which, it is suggested, might have been harmless had it taken place in the blood stream. In passive sensitization, conversely, no injury could result until considerable quantities of the antibody had become united to body cells in the course of several hours. That the antibody injected into passively sensitized animals indeed disappears from the circulation with relative speed, has been shown by Doerr and again recently by Weil.

Besredka's⁸ early hypothesis, too, though incorrect in most of its premises, assumed the necessity of the intervention of the body cell in anaphylaxis—an opinion here again largely based on the observed interval in passive sensitization, and the same idea occurs at about this time in the work of Doerr and Russ, who likewise conceived the process as taking place directly on the body cell.

It is true as Doerr²⁹ has pointed out in a recent summary of anaphylaxis, that these early hypotheses were for a time relegated to the background, yielding the prominent central position to opinions which held that anaphylactic shock was the result of intravascular parenteral digestion. To some degree this is due to the fact that Vaughan's work on the toxic protein split products and Friedemann and Friedberger's experiments on the production of similar poisons by purely biological methods, seemed to offer for the time being a field of work promising logical solution of this difficult problem. At the same time there was much evidence in the published work of such investigators as Friedemann, Scott, Briot, Biedl and Kraus, and Doerr himself which seemed to show clearly that the interval in passive sensitization was not an

28 Friedberger *Ztschr f Immunitätsforsch*, 1909, 11

29 Doerr *Ergebnisse der Immunitätsforschung*, edited by Weichhardt, Berlin, 1914, 1, 257

invariable necessity. Consequently and very naturally the early purely cellular conceptions were not accepted as telling the whole story, and a few observers allowed the pendulum to swing completely away from this point of view. Nevertheless it is not fair to say that during this time the cellular theories were entirely neglected. We do not believe that von Pirquet ever entirely abandoned his original opinion that there was involved in certain phases of anaphylaxis an "allergic" of the tissues. Moreover, it was during this period that those methods of research were first applied to anaphylaxis which furnished in principle and fact all the important premises for the present almost universal cellular point of view. I refer to the transfusion method as employed in anaphylactic dogs by Pearce and Eisenbrey³⁰ and the method of observing isolated tissues from anaphylactic animals as used by Schultz³¹—work which appeared as early as 1910. Pearce and Eisenbrey working with two normal and one sensitized dog, transfused the blood of one of the normal animals into the sensitized one, transferring the blood of the latter to the normal dog. "At the proper moment the normal dog containing the blood of the sensitized animal and the latter containing the blood of the normal dog, each received intravenously the toxic dose of horse serum." The normal dog having the sensitized blood did not react, the sensitized dog having the normal blood showed typical fall of blood pressure. Pearce and Eisenbrey drew the conclusion "that the phenomenon of anaphylaxis is due to a reaction in the fixed cells and not either primarily or secondarily in the blood."

In the same year Schultz began to work with what is now spoken of as the physiological method. He determined that smooth muscle—freshly excised from various animals—will react with contraction when brought into contact with serum. When such muscle was taken from anaphylactic animals after being thoroughly washed free of blood, it would react more energetically and to smaller amounts of the homologous serum. There are many interesting by-products of Schultz's work, such as the differences between fresh arterial blood and blood serum in their abilities to stimulate contraction, but this and other points will not be discussed at present. The important and incontrovertible fact established by Schultz is the changed reaction-energy or, in truth, "allergic" of the smooth muscle of anaphylactic animals to the stimulus of the sensitizing antigen. Dale³² has confirmed and extended these observations of Schultz. He removed the uteri from guinea-pigs after thoroughly perfusing them with Ringer's solution to remove all

30 Pearce and Eisenbrey *Congr Am Phys and Surg*, 1910, viii

31 Schultz *Jour Pharmacol and Exper Therap*, 1910, 1

32 Dale *Jour Pharmacol and Exper Therap*, 1913, iv

blood. He then suspended them in baths of Ringer's solution and by the customary physiological methods measured the contractions following the addition of various amounts of foreign protein in the form of—among other things—horse serum and beef serum. He found that the uterus of an animal sensitized to horse serum would react to this substance in dilutions of 1 2,000 or 1 10,000, while the organ taken from a normal guinea-pig reached its limit of reaction-ability at dilutions often less than 1 200. A uterus that had reacted strongly was found to be subsequently desensitized. A normal uterus could not—strangely—be passively sensitized by immersion into a solution containing serum antibodies. This method of investigation has recently, also, been taken up by Richard Weil³³ who has fully confirmed the principles laid down by Schultz and Dale. He has incidentally also answered an objection to the conclusions of Dale and Schultz (never indeed a very valid objection), namely, that the reaction of the muscle tissue of a sensitized animal might be in part due to the fact that the blood, i e, the antibodies, had not been entirely washed out of the tissue spaces by perfusion. Weil performed the very simple and ingenious experiment of injecting a normal guinea-pig with large amounts of immune serum (anti-horse serum) and after a few minutes killing the animal. He then suspended the uterus in Ringer's solution in the usual manner without washing it completely free of blood. Contact with the homologous antigen produced no response. We may accept as definitely established by these researches of Schultz, Dale and Weil that the fixed cells of anaphylactic animals possess an increased reaction-ability toward the antigen which is in no sense secondary to processes involving the circulating antibodies. Moreover, the work of Weil seems to indicate that desensitization of a passively prepared guinea-pig deprives the uterus of its power to respond and that the gradual spontaneous diminution of hypersusceptibility on the part of the guinea-pig is accompanied by an entirely parallel loss of reaction-capacity on the part of the isolated uterus.

The recent work of Coca,³⁴ too, has further fortified the cellular point of view by a method which in principle is similar to that employed by Pearce and Eisenbrey. Coca succeeded in perfusing actively and passively sensitized guinea-pigs with the defibrinated blood of normal guinea-pigs in such a way that the original blood of the sensitized animals was reduced to a necessarily slight residue. Animals so treated could be kept alive for as long as six hours after the trans-

33 Weil, R. Jour Med Research, 27, 1913, 30, 1914, Proc Soc Exper Biol and Med, 1914, xi, 86

34 Coca Ztschr f Immunitätsforsch, 1914, xx

fusions and remained delicately hypersusceptible in spite of the blood substitution

Limiting ourselves for the present to the phenomena of anaphylaxis in which noncellular antigens are employed, we may safely say that the evidence furnished by the incubation time necessary in passive anaphylaxis by the transfusion experiments of Peaice and Eisenbrey and of Coca, and most conclusively by the work on isolated tissue by Schultz, by Dale and by Weil, shows conclusively that the hypersusceptible state is largely determined by a changed reaction-capacity to the specific antigen on the part of the fixed tissue cells—an "alelgie" which is probably due to the presence of specific antibodies in the substance of the cell protoplasm, and incidentally accounts for such effects as the skin reactions. It is probable that the acute symptoms and death of anaphylactic guinea-pigs (and indeed of other animals) is in most cases of experimental anaphylaxis due to the reaction which takes place between the injected antigen and these sessile receptors.

So much we must logically accept. However, are we justified in denying all possibility of injury to the animal when antigen and antibody meet in the circulation? This is indeed the claim of a number of workers who are inclined to regard the presence of circulating antibodies not only as incapable of leading to injury, but in fact as a protection, in that the antigen is deflected by them from the antibodies united with the cells. Personally we believe that this radical cellular interpretation of all phases of the phenomena of anaphylaxis goes too far. It was shown by Friedemann as early as 1909 that typical anaphylactic reactions could be produced in rabbits when the antigen (beef serum) was injected simultaneously with or mixed with the serum of passively sensitized rabbits. Indeed Friedemann claimed that by this method severe and fatal reactions could be produced in rabbits more regularly than when an interval was observed. Richet in the same year reported experiments in which immediate symptoms were elicited in dogs injected with mixtures of crepitin and the serum of a crepitin-treated dog, the crepitin in quantities far below that necessary to elicit symptoms in itself. (In this experiment of Richet the crepitin and the serum were left in contact *in vitro* for 20 minutes, a fact which somewhat detracts from the direct bearing of this work on our present discussion.)

In 1910 Biedl and Kraus³⁵ obtained immediate and severe symptoms in guinea-pigs when they injected intravenously mixtures of horse serum together with the serum of sensitized guinea-pigs. Briot³⁶ in the same year obtained reactions in young rabbits into which he had

35 Biedl and Kraus *Ztschr f Immunitätsforsch*, 1910, iv

36 Briot *Compt rend Soc de biol*, 1910, lxxviii, 402

injected mixtures of horse serum and anti-horse serum Gurd³⁷ in a recent publication obtained reactions in guinea-pigs when he injected intravenously immune rabbit serum (anti-sheep serum) and immediately thereafter sheep serum We ourselves have been able to obtain occasional and distinct results in rabbits and guinea-pigs both by simultaneous and immediately consecutive intravenous injections of antigen and antibody, though we did not succeed in attempts to duplicate exactly the experiments of Friedemann and of Biedl and Kraus

We have here a not inconsiderable mass of evidence which points to the conclusion that the whole story of the anaphylactic phenomena cannot be told by the cellular conception alone, and that probably—as in immunity—both cellular and intravascular processes are involved Few thoughtful workers on hypersusceptibility would think of denying at present the probably predominating cellular factor in the ordinary anaphylactic type-experiment I may say that many of us have never doubted that this element was an undeniably important one in serum anaphylaxis since the time when the experiments of Pearce and Eisenbrey and those of Schultz confirmed the suggestion of this conception forced on us by the incubation time in passive sensitization and the studies of von Pirquet We do not share, however, the exclusively cellular view recently advocated in a recent summary and apparently accepted by Doerr, one of the most capable students of this subject

It is true that almost all of the workers cited above as having obtained passive sensitization, without the interval, admit the irregularity of such results, and Friedemann, Gurd and others call particular attention to the great importance of the relative amounts of antigen and antibody when these are injected together or in rapid sequence This has been our own experience and although we have obtained very definite reactions in this way, we feel that in any given experiment success or failure cannot be as regularly foretold as in the experiments in which the interval is allowed Moreover, the reactions obtained by these methods are often mild—delayed—and are rarely violent or rapidly fatal We ourselves have never obtained a fatal result Yet it is idle to say—as has been said—that the reactions so obtained are accidents, probably due to secondary factors, negligible in formulating a conception of anaphylaxis There is no such thing as an accident in nature, and the observation, though irregular and depending on elements in the experimental procedures not easily amenable to control, has been made too often and independently by a number of different trained observers to be thrown out of consideration in a theoretical scheme which is to be just to all the facts

37 Gurd Jour Med Research, 1914, xxxi, 205

Since we cannot, therefore, deny that under certain circumstances injury to the animal may result from the meeting of the antigen and antibody within the circulation, how are we going to account for the fact that such reactions are difficult to obtain and cannot be obtained with regularity? This question is not a simple one but it is our own opinion that a possible explanation may be found in the failure of rapid union of antigen and antibody in the blood stream. We have already mentioned that all observers who have experimented along these lines have found that very definite proportions between antigen and antibody govern the success of such attempts and that with each lot of serum and anti-serum the optimum proportions must be determined by experiment. In Friedemann's work on rabbits he found that the relative amounts of antigen and antibody which produce reactions in his rabbits if injected together corresponded roughly to the proportions which *in vitro* gave precipitates. An excess of one or the other substance would prevent reaction or at least result in a negative experiment. Now it is well known to all who have worked with antiprotein serums that the precipitin reaction can be inhibited by an excess of one or the other reagent.

When a constant amount of precipitating serum is used, the most prompt and voluminous precipitation may, for instance, occur when the antigen dilution is 1:50, and both the speed and the amount of precipitate may diminish not only as this dilution is increased, but also as the concentration is increased. This is a phenomenon which is common to all colloidal reactions and the mutual precipitation of the two colloids is to a large extent dependent on relative proportions.

It is a well-known fact (also familiar to many of you) that Linossier and Lemoine,³⁸ Eisenberg,³⁹ Ascoli,⁴⁰ von Dungern⁴¹ and others have frequently noticed that animals treated with a foreign protein such as horse serum, for instance, may contain in their blood serum, as late as six, seven, eight or more days after injection, both the antigen and its antibody ununited and separated. Thus we have often seen ourselves, if we bleed an animal that has been rapidly treated with such a foreign protein, that its serum will precipitate horse serum, and will at the same time be precipitated by anti-horse serum taken from another rabbit. It is thus plain that the serum in the case mentioned contains not only horse serum as such (a remnant of that injected) but also antibodies against horse serum which have been formed in response to the injection. It is unquestionable from the experiments of others and from our own extensive confirmation, that

38 Linossier and Lemoine. *Compt rend Soc de biol*, 1902, liv, 85

39 Eisenberg, P. *Centralbl f Bakteriöl*, 1903, Orig, xxxiv, Part 1, p 259

40 Ascoli, M. *Munchen med Wchnschr*, 1902, xlix, 1409

41 V. Dungern. *Centralbl f Bakteriöl*, 1903, Orig, xxxiv, Part 1, p 355

the serum of such an animal may contain side by side free antigen and free antibody. Why have these failed to unite? If such a serum is allowed to stand at room temperature or in the ice box there will take place a very slow precipitation and a concomitant diminution in the amount of precipitin present. The precipitate thus formed has slight and distinct complement-fixing properties. Slow union, therefore, is taking place.

Another strange fact about such serums is that if two such rabbits are prepared, in each of which both free antigen and antibody can be determined, these serums when mixed will promptly precipitate each other.

A number of explanations have been advanced for the simultaneous presence of antigen and antibody in the same serum without union. Eisenberg and Volk have attempted to explain it by dissociation—that is the antigen and antibody are present united and also dissociated, reacting according to the laws of mass action. This has seemed to us unlikely. For, were this the case, the serum, as taken, should in itself exert definite complement-binding properties, since on the basis of this explanation it must contain not only the two reagents separate but a rather large proportion of the antigen-antibody complex united. This is not the case according to our own observations and according to similar ones made by Gay and Rusk.

Von Dungern⁴² has assumed that the state of affairs described was due to the fact that the antigen might contain a number of different substances, alpha, beta, etc., each of which produces its own specific *Teil-precipitin*. He believes it possible that at certain stages in the immunization the free antigen present might be, say, an alpha fraction, the free antibody, let us say, a beta precipitin, the two not fitting and therefore unable to react.

Auch hier handelt es sich nicht um zwei reaktionsfähige Körper, deren Verbindung aus irgend Gründen unterbleibt, sondern um Substanzen, welche keiner Affinität zueinander besitzen. Die betreffenden Kaninchen haben zu dieser Zeit noch nicht alle möglichen Teilpräzipitine gebildet, sondern nur einzelner derselben. Diese zunächst produzierten, nur auf bestimmte Gruppen der präzipitablen Eiweisskörper passenden Partialpräzipitine sind es, welche nach der Absättigung aller zur Verfügung stehenden zugehörigen Gruppen der präzipitablen Substanz im Serum nachweisbar werden. Daneben bleibt aber ein anderer Teil der präzipitablen Substanz, der keiner Affinität zu dem gebildeten Präzipitin besitzt, bestehen, solange bis ein anderes Partialpräzipitin von den Kaninchenzellen geliefert wird, welches sich mit Gruppen der in Lösung gebliebenen Eiweisskörper vereinigen kann.

This has not seemed likely to us although they are clear when taken and remain so for considerable periods, but do eventually precipitate

42 Von Dungern. Centralbl. f. Bacteriol., 1903, xxxiv, first part orig.

slowly and in the course of days, an observation made not only by us but by Merckel

It has seemed to us most likely that there might be in the circulation of animals an inhibiting agent, somewhat in the nature of a protective colloid, which prevented the union of antigen and antibody, or at least tended to make it an extremely slow process

We may assume in the light of our present knowledge that both the antigen and the antibody are colloidal in nature, and together with Stuart W. Young,⁴³ we have been able to produce an analogy to the condition found in the serums just described by using three colloidal suspensions, that is, arsenic trisulphid, gelatin and gum arabic. Emulsions of gelatin flocculate suspensions of arsenic trisulphid; if small amounts of gum arabic are added flocculation is prevented. In order that a protected suspension shall be produced in which no precipitation will occur very definite proportions between the three suspensions must be arrived at, but a number of quantitatively varying mixtures of the three can be produced which will hold up without precipitating for a considerable period. Like the serums described above, two such suspensions in which the relative proportions of the three are not the same will precipitate each other when by rapid mixing the quantitative relationship necessary for protection is suddenly disturbed.

We have here, then, a complex analogy to the conditions in the serums. Two substances, mutually flocculable, do not precipitate. They are prevented from precipitating by the presence of a third substance which "protects" when certain definite proportions between the three are maintained. Many quantitatively different mixtures of this kind may be made in which flocculation is in this way prevented. Mix two such protected mixtures, disturb these proportions and flocculation occurs, faster or slower according to the relations arrived at in the mixtures.

Moreover Porges⁴⁴ has shown that the factor of colloidal protection may well play a part in the occurrences taking place in a medium of blood plasma or serum. He has found that fresh native serum will precipitate mastic emulsions. The same serum heated, if used in very small quantities, will protect mastic emulsions against precipitation of the fresh serum. This alone shows what delicate physical changes in the body fluids may make for fundamental changes of reactions.

In our own experience these experiments of Porges were in principle confirmed, small quantities of heated dog serum added to arsenic

⁴³ Zinsser and Young. On the Possible Importance of Colloidal Protection in Certain Phases of the Precipitation Reaction, *Jour. Exper. Med.*, 1913, xvii, 396.

⁴⁴ Porges, O. In Kraus and Levaditi. *Handb. d. Technik u. Methodik der Imm.*, Jena, 1909, ii, 1146.

trisulphid precipitated this suspension, slightly greater quantities again dispersed it. Of similar significance are experiments by Streng on the so-called *conglutinins*, substances in serum which are supposed to produce an agglutination of blood corpuscles or bacteria which have been previously treated with fresh serum or alexin. The addition of minute quantities of alexin to typhoid bacilli and agglutinin prevents agglutination.

Friedemann,⁴⁵ furthermore, a pioneer in this branch of serum investigation, in studies on the serum reactions has come to the conclusion that certain anticomplementary activities of the serum globulins may be inhibited by the albumins of the same serum. Schmidt⁴⁶ speaks of a similar *Schutzwirkung* on the albumin of normal serum. When lues serum was mixed with certain lipid extracts (of human heart, used for Wassermann antigen) precipitation resulted. Such precipitation was brought about also by the globulins of normal serum—but was prevented or “protected against” when the albumin of normal serum was added to the mixtures. Friedemann himself (and Schmidt agrees with him on the main points) thinks that the globulins and albumins of normal serum are in antagonism, the albumins preventing certain reactions (such as complement fixation) in which the former become active as soon as the albumins are removed or diminished.

We do not have to force analogy to look on such serum reactions as essentially following laws similar to those observed in the case of chemically definable colloids. Apart from the protein character of serum constituents, we know that serum reactions follow quantitative laws analogous to those observed in colloidal reactions (inhibition zones, etc.). We know the importance of the electrolytes in the phenomena, we know that the immune bodies like the colloids diffuse but slowly, and we know from the work of Landsteiner and Pauli⁴⁷ especially, that certain serum hemagglutinins will wander, like other colloidal substances, to one pole or the other when a direct electric current is passing through solutions containing them, like amphoteric substances changing the direction of wandering according to the alkalinity or acidity of the menstruum. The points of similarity are too numerous to be exhaustively reviewed in this connection. They are so many and so striking, however, that we should hesitate to apply any explanation to serum phenomena of any kind which is not in accord with the general behavior of colloids.

In recent experiments of our own, moreover, we have been able to show that when precipitation reactions are set up in comparative series,

45 Friedemann. *Ztschr. f. Hyg.*, 1910, lxvii.

46 Schmidt. *Ztschr. f. Hyg.*, 1911, lxix.

47 Landsteiner and Pauli. Cited from Landsteiner, “Colloide u. Lipptide in der Immunität,” from *Kolle und Wassermann*, Ed. 2, ii, 1244.

in one case using the globulins of normal rabbit serum, in salt solution, as the diluent for the antigen, and in another series the albumins of the same serum, the reactions in the latter are noticeably slower than in the former—than similar reactions in salt solution or in active or inactive serum. There is apparent inhibition of the reaction by the serum-albumin.

Enough has been said to show the justification of any theory which utilizes as a major premise the possibility of the participation of protective colloids in reactions taking place within the vessels of an animal. We suggested some years ago in a paper on this subject that it was such a protective colloidal action in the plasma of animals which prevented the rapid union of antigen and antibody in the blood stream, and we thought at the time that such an arrangement would indeed constitute an automatic protection of animals against sudden and severe injury when a foreign protein gained entrance to the blood stream. Our conception of the whole process would therefore be something as follows. The injection of a foreign antigen into the animal body leads it to antibody formation by the tissue cells. These antibodies are in part discharged in the blood stream and in part sessile on the cells. There is a gradual union between the circulating antigen and antibody and probably between the circulating antigen and the sessile antibodies. Under conditions apt to occur in the course of normal conditions the quantity of antigen which gains entrance is small and no injury results from such union by which probably a gradual parenteral digestion of the foreign substances is obtained. When in the course of abnormal states, infectious disease, etc., a situation arises in which considerable amounts of antibody have been formed and relatively large amounts of antigen are also present, all the conditions are furnished for what we call anaphylactic injury, unless there were some efforts to prevent the rapid union in these antibodies. In the anaphylactic experiment we see that the rapid union of antigen and antibody on the cell will kill. But it is likely that in most cases during immunization the circulating antibodies are far in excess of those still sessile on the cells, and were rapid union between these and the antigen not inhibited in the circulation, the animal would be constantly and severely ill during all processes of immunization. However, we know that in highly immunized animals antigen and antibody may be present side by side ununited. Is it not necessary to assume that this is evidence of a protective inhibition of union? For the colloidal protection would lead to a very slow union, in which, because of the gradual nature of the process, practically no severe injury of the individual could result. According to this conception we can quite easily explain why the simultaneous injection of antigen and antibody into the normal animal

would result ordinarily in slight and delayed symptoms. Accidental success in so balancing the proportions that complete elimination of protection results would account for the occasional acute symptoms and death observed in such procedures. It is quite clear that such an ideal experiment cannot be regularly obtained, for the simple reason that the protective element may be subject to variation, and since there are so many secondary factors even in test tube experiments on precipitation which influence such reactions.

When the animal is sensitized by the methods of the classical anaphylactic experiment, the union in the cells, violent and stormy, results in death after anaphylactic shock, and whatever symptoms might have resulted from the union of the two substances in the blood serum are overshadowed and secondary.

It is perfectly clear that there are many gaps in the absolute experimental proof of such a conception. We know, however, that slow, gradual and acute injury may follow on the simultaneous interaction of antigen and antibody in the animal body. We know from the many experiments of Vaughan, Friedberger and of others that *in vitro* such a meeting in the presence of active serum can result in the production of injurious substances which produce anaphylaxis-like symptoms when injected into the animal. We know from the experiments of Doerr that the injection of formed precipitates will injure. Whatever we may think about the nature of the poison and its mechanism of production there is little reason to doubt that the noxious agent can be produced without reference to the body cells. And we believe from this, together with the premises on which we have developed our idea of colloidal protection, that such a conception may form a perfectly legitimate explanation for the scattered and yet definite observations made since Friedemann, by many others and by ourselves, of immediate symptoms after simultaneous injection of antigen and antibody.

VI

In discussing the probable localization of anaphylactic reactions in the preceding paragraphs, we limited ourselves entirely to the phenomena occurring when sensitization is carried out with noncellular substances such as blood serum, egg albumin, etc.

When the antigen employed is cellular, consisting of bacteria or red blood cells, we are confronted with a problem of considerably greater complexity. As morphologically compact structures these cells cannot enter into direct chemical relations with the fixed tissue cells until they have been either disintegrated or at least have given up constituents to solution in the blood plasma. In consequence we must assume two separate phases of all such reactions—one the occurrences within the

circulating blood in which the injected cells come in contact with the solvent elements of the plasma and during which the solution of antigenic constituents is brought about, the other the subsequent reactions entered into by these dissolved substances, either within the circulation or on the fixed tissue cells with their respective receptors or antibodies

If therefore Doerr²⁰ and others (Denzer and Weil) claim that anaphylaxis with cellular antigens is entirely similar in principle to that produced with dissolved, unformed antigens, they may well be perfectly right in so far as the second phase of these phenomena is concerned. They found that guinea-pigs injected with hemolytic serums reacted to the injection of the blood cells when, as in passive serum anaphylaxis, a latent period or interval was allowed to elapse between the administration of the antibodies and that of the nitrogen. This means simply that they failed to obtain acute or marked symptoms (for quantitative reasons possibly) when the cells and antibodies met in the blood stream.

Analyzing the phenomena in this way it becomes clear that when we inject cellular material we are merely injecting an antigen—or more probably a group of antigens—enclosed in the morphological structures of the cell, and amenable to reaction only after liberation. After this has taken place, subsequent occurrences should in no important principle differ from those following on the injection of an unformed substance like serum, or we may say for the sake of clearness, a predissolved antigen, and all that we have said about such conditions in our preceding discussion should apply here.

Added to this, however, we have in the case of cellular antigens a process unnecessary when unformed antigens are injected, namely, the cytolytic or cytotoxic reaction which precedes the liberation of the cell-constituents, and in the course of which the formed elements are broken up. And we need only compare the slow autolytic disintegration of cells in sterile inactive serum or salt solution with the rapid changes occurring in active hemolytic or, in certain cases, in bacteriolytic serums, to be convinced that such disintegration is due to reaction with active serum constituents.

We may logically accept, then, that by injecting cells, we are for one thing injecting substances which will, in part, soon be liberated and which will call forth all the changes and enter into all the reactions which are associated with the injection of dissolved antigens. In addition to this, however, we are confronted with a further problem. Is there injury to the animal body, comparable in broad principles with anaphylaxis, during this intravascular reaction between whole cell and

cytolytic antibodies which precedes the liberation of the soluble constituents? Is there, in other words, a true "cell anaphylaxis"?

Since it is probable that the principles of cellular anaphylaxis are the same whatever the variety of cell employed, we may take red cell hypersusceptibility as a basis for discussion. It is a well-known fact, long recognized, that a serum which is capable of hemolyzing the red cells of any species is toxic when injected into an animal of this species. This is true not only of hemolytic serums but also of such normal serums which like, let us say, goat serum and rabbit cells, can hemolyze normally the red cells of another animal. Since occasionally the serum of an individual of one species can so act on the red cells of another individual of the same species, our surgeons call for careful investigation of receptor and donor before performing transfusion. The injection of such a serum intravenously may kill with symptoms not unlike anaphylactic shock. Here it is often difficult, as we shall see (or indeed it may be impossible), to determine, whether such death is truly anaphylactic in nature or whether it is due to clumping of red cells or hemagglutination, a property which is very often an accompaniment of hemolytic power. However, hemagglutinating properties cannot be held responsible for the edema and localized injury which, as Uhlenhuth and Haendel have shown, may follow the subcutaneous injection of such serums. It thus appears as though the process of hemolysis were accompanied by the liberation of injurious products.

The first systematic investigation of red cell anaphylaxis was undertaken by Ulrich Friedemann¹¹. Friedemann injected washed beef cells into rabbits and followed this by a second injection after from seven days to three weeks. Rabbits so treated showed the symptoms ordinarily associated with anaphylaxis in these animals. Active sensitization seems thus to have been accomplished with beef cells. Schiff and Moore have recently suggested that Friedemann really obtained serum anaphylaxis, but since Friedemann explicitly states that he worked with washed cells, we can see no just reason for such an assumption. Another objection to Friedemann's results, however, is possible—one which is far less easy to controvert—namely, that the illness of his rabbits may have been due to hemagglutination, which by itself may produce serious illness or even death by mechanical obstruction of blood vessels. Friedemann, indeed, takes cognizance of this possibility but makes no attempts to rule it out in his experiments. As a matter of fact we think it unlikely that hemagglutination played a part in his rabbits, but the possibility cannot be excluded. We will revert to this particular question.

Passive sensitization was produced by Friedemann against beef cells in rabbits by injecting the specific hemolytic serum. He obtained

his best results when he injected serum and cells together, mixed *in vitro*. However, he also obtained positive experiments when the two were simultaneously injected into opposite veins. His results were inconstant when he allowed an interval to elapse between serum and cell injection—a fact which argued for the direct occurrence of the reaction within the circulation.

Most important of all, Friedemann mixed hemolytic serum and cells in test tubes, letting them stand for five minutes in a water bath and then, before any considerable degree of hemolysis had taken place, he centrifugalized and injected the faintly red supernatant fluid into rabbits. A rabbit so injected became extremely ill and many of them died after shorter or longer intervals, with symptoms typical of anaphylaxis in rabbits. Friedemann concluded that when red cells came in contact with hemolytic antiserum, poisonous substances were liberated, even before actual hemolysis had taken place, and that these toxic products were responsible for the subsequent injury to the animal. He identified the anaphylactic antibody with the hemolysin. This view, therefore, is identical in principle with the one we have discussed as the conception of parenteral digestion. Indeed Friedemann's experiments furnished the point of departure for Friedberger's subsequent work on the so-called "anaphylatoxins."

Doerr and Moldovan,⁴⁸ a little later (1910), studied the effects of the injection of serums hemolytic for guinea-pig erythrocytes into guinea-pigs, and drew conclusions which substantiated those of Friedemann. They found that the toxic effect was due to the action of the hemolytic serums on the guinea-pig erythrocytes. Toxicity could be removed from such serums by absorption with these cells, and the toxic products could be produced by contact of serum and cells *in vitro*. From these experiments, again, it seemed that the liberation of a toxic substance followed on contact between erythrocytes and specific antibodies, whether this contact took place within the circulation or in the test tube. That the antibodies concerned need not necessarily be identical with hemolysins themselves follows, we think, from the work of Doerr and Moldovan as well as from work of our own on the toxicity of certain normal serums⁴⁹—experiments which could not be discussed in detail without taking more space than seems justified.

Although much irregularity of result has been obtained in the production of active erythrocyte anaphylaxis in both guinea-pig and rabbit experiments, nevertheless, it seems clearly established that acute death does follow the repeated injection of such cells when dosage and interval are properly observed. The recent experiments of Schiff and

⁴⁸ Doerr and Moldovan. *Ztschr. f. Immunitätsforsch.*, 1910, vii.

⁴⁹ Zinsser. *Jour. Exper. Med.*, 1911, xiv, No. 1.

Moore,⁵⁰ though they clearly illustrate the difficulties of such procedure in guinea-pigs, still record a sufficient number of positive results to reconfirm its actual occurrence. From one of these experiments, indeed, as well as from the experience of Friedemann and others with passive sensitization by antierythrocyte serums, it would appear that with red cells the phenomenon requires a procedure differing from that successful with serum anaphylaxis, in that a considerable concentration of antibodies is needed, i e, a condition calling in the active experiment for more than one preparatory injection, or, in the passive sensitization, for the injection of a serum of high potency. This, as we know, is the case, also, in bacterial anaphylaxis, in which experiments are usually successful only if many and repeated preparatory injections are made. It is this factor, possibly, which may account for the failure of so many workers to obtain true cell anaphylaxis when they have followed the technic successful in the serum experiments—i e, that of only one preliminary sensitizing dose—or that, in the passive experiment, many have failed to duplicate Friedemann's success when both antigen and sensitizer were simultaneously injected. It is more than likely that a weak sensitization and consequently a slow reaction between the cells and the antiserum may be interrupted by prompt phagocytosis of the injected cells, with consequent protection against the further developments of the process.

It is true that in many cases of erythrocyte anaphylaxis it may be impossible to say with certainty whether death was due to true shock or whether it was caused by embolic processes due to hemagglutination. This possibility has not been ruled out in many otherwise complete investigations—though in experiments like those of Friedemann and Amako⁵¹ it seems but a remote possibility. However, in individual instances, such as our own experiments with normally toxic serum, it has been shown that the toxicity may disappear with inactivation, though hemagglutinating properties are retained, and it seems that, to kill acutely hemagglutination must be rapid, powerful and extensive. Moreover, the speed and completeness of recovery showing non-lethal degrees of erythrocyte anaphylaxis argues at least against the frequent occurrence of hemagglutinative death by embolism in experiments carried out in this way. The local injury following the subcutaneous injections of normal and immune hemolytic serums must of course occur entirely independent of hemagglutination. Finally, the fact that contact of the cells with active serum—as first carried out by Friedemann—produces a poison *in vitro* which kills acutely with symptoms of anaphylaxis, seems to render fairly certain the assumption that

50 Schiff and Moore. *Ztschr f Immunitätsforsch*, 1914, xxii

51 Amako. *Ztschr f Immunitätsforsch*, 1914, xxii

similar contact in the circulation may lead to like result. For we know that the entire process of hemolysis can take place intravascularly.

Whether the antibodies that so react with the cells are the hemolysins themselves, is a question that we hardly have the time to discuss and which moreover is merely an incidental one. After all, hemolysis itself is merely one visible result of a reaction which probably affects profoundly the entire cell structure. About bacterial anaphylaxis our knowledge is still more defective than is that occurring when erythrocytes are used. We do know, however, that active sensitization with bacterial proteins and with whole bacteria is possible—though many injections are apparently necessary—the exact procedure being subject to so many fortuitous influences that so far no regularly successful method can be outlined. We also know that, as with red cells, contact between the bacteria and active serums will result in the production of acutely toxic substances—which we have discussed above as “proteotoxins.”

SUMMARY

We may summarize our views on cell anaphylaxis, briefly, as follows. When whole cells are injected into an animal two distinct processes are set in motion. First, the formed cells come into relation with circulating antibodies. During this contact toxic substances—“proteotoxins”—may be set free if quantitative relations are suitable and cells sufficiently sensitized. Where the matrix of the poison is found and to what an extent the complement participates—these are in many respects still open questions. This reaction alone, if sufficiently vigorous, may cause acute symptoms and even death.

During this reaction antigenic cell constituents are set free to solution and these then enter into reaction with their respective antibodies or receptors in the blood or on the fixed cells. The last-named reactions are entirely comparable to those of serum anaphylaxis and have been sufficiently discussed.

Whether in the first-named process, when the whole cell meets its antibody in the blood stream, we regard the poison as originating from the matrix of the antigen or from the serum itself by the withdrawal of antienzymes is immaterial. The reaction is subject to so many modifying factors that experimental control is made difficult and results cannot at present be so regularly foretold as is the case in serum anaphylaxis. It seems probable from the work of Friedberger and others that a delicately balanced optimum proportion between antigenic cells and antibodies must be obtained. Moreover, unless the process is rapid and harmful effects very sudden, prompt phagocytosis of the cellular elements may remove the antigen from further reaction possibility.

It is plain that such a conception has the greatest importance in the understanding of infectious diseases. When bacteria form the antigen which gains entrance to the animal body, the gradual stimulation of specific antibodies in the animal may eventually lead to such a two-phase reaction. Specific sensitizers or amboceptors (cytotoxins) are gradually formed and these may react with the dead and the living micro-organisms. There may be a direct formation of proteotoxins and at the same time a liberation of soluble antigen from the bacteria. It may be, as von Pirquet has suggested, that the sufficient establishment of such reactions between cell and antibody may mark the end of what we speak of as "incubation time," no noticeable time accruing to the animal body until the antigen-antibody reaction has been initiated. The "proteotoxins" so formed, whatever their matrix, may then, as we have shown with Dr. Dwyer, act as aggressins, lead to a leukopenia, as in typhoid fever, and thereby increase indirectly the invasive capacity of the micro-organisms. The antigenic substances which have gone into solution may at the same time react both on the fixed cells with sessile receptors, and, to a merely incidental degree, with their receptive circulating antibodies, adding thereby to the injury sustained by the host.

True immunity against dissolved antigens, we have stated in the beginning, probably does not exist, for animals having high antibody contents in their serum may still die suddenly with convulsions after a fourth or fifth injection with foreign serum. In the case of cellular antigens, however, and especially bacteria, true immunity may exist in two forms. On the one hand if the animal possesses a high concentration of antibodies before the micro-organisms have gained entrance, an immediate bactericidal effect may prevent their multiplication, the harmful effects resulting from the union of the small initial amounts of antigen and antibody being so slight as to be unnoticeable. Again, after the bacteria have gained entrance, if the quantitative relations between antigen and antibody are such that the reaction is either slight or for purely quantitative reasons results in little injury for the time being, then sensitization of the bacteria or other cells by the antibodies, leads to rapid phagocytosis. And this process of phagocytosis represents true immunity, a removal of bacteria incidental to which there is, as far as we know, no injury to the host. It is in the process of phagocytic removal, chiefly, in which the reaction to cell injection differs from that taking place in response to the administration of unformed protein. It may be this element which renders it so difficult to obtain sharp anaphylactic reactions with cellular antigens. And it is the absence of phagocytosis in the latter case which probably prevents the existence of a true immunity.

AMAUROTIC IDIOCY *

GENERAL AND HISTORICAL CONSIDERATIONS WITH REPORT OF A CASE

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Amaurotic familial idiocy—a clinical entity of which about one hundred cases are on record, is of great interest to the general medical profession because its symptoms are relatively so definite but rarely so correlated by the observer as to be recognized as the disease we are about to discuss

The forerunners of the discovery of this disease were the ophthalmologists, chief of whom was Warren Tay,¹ who, in 1881, published an article under the caption "Symmetrical Changes in the Region of the Yellow Spot in Each Eye of an Infant." Tay found that in his patient, a child of 12 months, in the region of the macula, there was a large whitish patch, in the center of which was a brownish red spot similar to that caused by embolism of the central artery of the retina. He considered this change probably a local congenital disturbance. Later, in 1884, he reported² three more cases with the same condition in the same family, all of whom died at 2 years of age.

Three years later B. Sachs³ made his noteworthy observations on the character of this disease in a paper on "Arrested Cerebral Development." In 1892 he reported a second case in the same family. Both children died at 2 years, had the same clinical symptoms and signs, and the brain of each showed the same pathologic changes. Sachs could give no explanation of the causes of this disease but said they were probably fetal-agenic.

Carter⁴ first recognized that the cases thus far corresponding to Sachs' were of Hebraic extraction and that "while to date, the majority of the cases reported belong to that race, by no means do all."

The term "amaurotic family idiocy" was proposed by Sachs in 1896, when the familial character of this disease was almost uniformly found. To this time 19 cases were described as having occurred in ten families. Combining the symptoms of all the cases

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1 Tay, Warren. Tr. Ophth. Soc. United Kingdom, 1881, i, 55

2 Tay, Warren. Tr. Ophth. Soc. United Kingdom, 1884, iv

3 Sachs, B. Jour. Nerv. and Ment. Dis., 1887, xiv, 541

4 Carter. Knapp's Arch. Ophth. and Otol., 1894, xxiii, 126

then known Sachs was able to arrive at a definite symptom-complex which he says is pathognomonic

- 1 Mental impairment in first few months of life leading to absolute idiocy
- 2 Paresis or paralysis of the greater part of the body—flaccid or spastic in type
- 3 Reflexes may be deficient or increased
- 4 A diminution of the vision, terminating in absolute blindness (changes in the macula lutea and later an optic-nerve atrophy)
- 5 Marasmus and a fatal termination as a rule about the second year
- 6 The occurrence of the affection in several members of the same family
- 7 Healthy at birth, remaining so up to the third or fifth month, and occasionally —
- 8 Nystagmus
- 9 Strabismus
- 10 Hyperacuity of hearing
- 11 Inordinate laughter was present in one case, and
- 12 Disturbances in deglutition were occasionally observed in others

This syndrome then, as described by Sachs, is one made up of a number of symptoms most of which occur in many other organic nervous diseases, but chief stress up to this time was placed on its familial character, racial predisposition and the fact that it occurred shortly after birth

It remained for Vogt⁵ in 1905 to describe a condition in young children similar to that which Sachs described in infants. This author considered these juvenile cases a separate entity and he proposed the term "juvenile family amaurotic idiocy" for them. The findings in his patients were that the disease is familial in character, has no predilection to the Jewish race, begins in early youth, leads slowly to blindness, frequently to paralysis, and death occurs after several years.

Vogt had six cases (two in one family, one in the second and three in the third) in all of which the children were normal to the fourth to seventh year when there was gradual onset of blindness with optic-nerve atrophy (one case showed frequent deposits in the retina), dementia, paralysis and death from two to fifteen months later.

Vogt states that he believes Tay-Sachs' disease and the juvenile form of family amaurotic idiocy represent different degrees of the same process, but that Tay-Sachs' disease is so sharply characteristic that it may well retain its name.

Soon after this Batten⁶ described two more cases of the juvenile type, one patient having "fits," together with dementia and retinal changes. His patients, like most of those cited above, died of marasmus.

5 Vogt *Monatschr f Psych u Neur*, 1903, xviii, 163, 320

6 Batten *Tr Ophth Soc United Kingdom*, 1903, xxiii, 386

Mayon,⁷ Higier,⁸ Ichikawa,⁹ Wandless,¹⁰ Dercum,¹¹ Turner,¹² Gordon¹³ and others have added materially to this list so that now there are probably about thirty cases of the juvenile type on record

In a paper of this character a paraphrase of each case would be out of place, but a combination symptom-complex of the reported cases shows normal growth and development until 3 years or later, failing mentality and sight (with gradual optic-nerve atrophy and retinal changes), gradual onset of paralysis (flaccid or spastic), with or without convulsions, irritability of temperament, nystagmus, familial tendency without predilection to the Jewish race, death usually from marasmus



Fig 1—Patient D F, aged 7 months

The following clinical and pathologic report of the author's case may serve further to emphasize the close relationship between the two types of amaurotic idiocy

D F, a girl, aged 6, entered the Children's Hospital because of "fits" Neither her parents nor any of her antecedents were of Hebraic extraction Both parents are living and well and are not related The daughter of a maternal uncle "had no control of her body at birth and died of brain trouble at between 4 and 6 months" A maternal granduncle died of "brain fever" at 14 years There is no specific history in either parent The Wassermann test in the mother's serum was negative She had one miscarriage but no stillbirths The patient was born at full term after a two-days' labor terminating with a hard, high forceps delivery The child was fed with proprietary foods from the first and never nursed Its mother claims that the infant was kept

7 Mayon *Tr Ophth Soc United Kingdom*, 1904, xxiv, 142

8 Higier *Deutsch Ztschr f Nervenheilk*, ix, 1

9 Ichikawa *Klin Monatsbl f Augenheilk*, 1909, xlvii, 73, 432

10 Wandless *New York Med Jour*, 1909, lxxxix, 953

11 Dercum *Jour Nerv and Ment Dis*, 1897, xxiv, 396

12 Turner *Brit Jour Child. Dis*, 1912, ix, 193

13 Gordon *New York Med Jour*, 1907, lxxxv

drunk with gin for the first month of life. She was a fat but not strong child. A severe attack of pertussis occurred in the second year, but subsided without complications. This was soon followed by "inflammation of the bowels" with high temperature, but recovery was complete.

From 2 to 2½ years the patient ran, played and talked — an active, healthy, apparently normal child. (See Figs 1, 2 and 3.)

At 3 she had "black measles." This was followed by "food poisoning" after eating canned deviled ham. The patient nearly succumbed. About three months later she had an attack of "indigestion" accompanied by unconsciousness and stiffness of the whole body. Recovery ensued which was followed by the measles.

Just about this time (age 3½ years) the mother noticed that the child had a slight limp. A chiropractic physician was called who found the hip was "out" about one-half inch. This he replaced without benefit to the child.

The patient's eyes began to "wander with a bewildered look" and a few days later she awakened with "attacks of crying and trembling and rigidity of the arms and legs which lasted for a few minutes." These attacks increased in frequency, as many as twenty a day being noted. Sometimes one side alone, sometimes both sides, and at others the head or arms alone were convulsed.



Fig 2—Patient D F, aged 9 months

After some of these attacks the patient showed strabismus the rest of the day. A sudden noise or jar would bring on a "spasm."

Because of increasing rigidity, which became rather constant about six months after onset, the patient was unable to help or feed herself and could not walk. From a bright, healthy, active child within six to eight months she became a dull, apathetic, inactive invalid who gradually ceased to notice objects about her. (See Fig 4.) The bowels were obstipated, necessitating daily enemas. Urination was involuntary.

Three years after the onset of the disease the patient presented the following positive findings:

A poorly nourished girl, only the purely vegetative functions persisted. Uncovering the patient or even clapping the hands in the vicinity of the bed, slamming the doors, etc., caused marked convulsive movements of the extremities and opisthotonus which lasted from ten to fifteen seconds.

There was a striking growth of hair on the extensor surfaces of the arms, legs and labia majora and the upper part of the back. The average length of these hairs measured three-fourths of an inch. The hair generally was thick and moist.

No scars or eruptions were present but the skin of the neck was deeply pigmented

No cranial deformities were present

Eyes The child was blind. No spontaneous nystagmus or ocular palsies were noted. The left pupil was larger than the right, both reacted very sluggishly to light and measured from 4 to 5 mm. Bilateral optic atrophy was present and the retinal vessels were very narrow. In the region of each macula there was a grayish-white area in which was seen a small brownish-red spot. The retina, besides being very thin, showed no deposits or abnormal changes elsewhere. This finding was confirmed later by Dr. L. D. Green.

Ears These showed marked hyperacuity of hearing. No visible pathologic changes were noted.

Mouth The upper incisors were separated 3 mm. No anomalies of dentition were present. The palate was high arched. Frequent gnashing of teeth (trismus) occurred during examination.

Glands The thyroid and thymus were small, the pectoral and posterior cervicals shotty, the inguinals large.

Chest The lungs and heart were negative. The abdomen also was negative.



Fig. 3—Patient D. F., aged 13 months

Spine With the patient in the sitting position the head fell forward, backward or laterally. The spine was very rigid on attempt at flexion or extension, but otherwise negative.

Extremities Marked diplegia of spastic type was noted.

Upper extremities Attitude—the fingers were flexed on the hands, the hands on the forearms. The forearms were flexed on the arms and everted. Attempts at pronation and supination were difficult. Passive movements were resisted but were not painful. The pectorals were tense. Placed in extension, the arms gradually assumed the position described above.

Lower extremities Very spastic and held in forced extension with the feet in equinovarus position. The Kernig sign was positive. The vasomotor system showed acrocyanosis. There was a general bluish mottling of the skin.

Reflexes These were everywhere much increased. Dorsal flexion of great toes occurred on plantar stimulation. No clonus was elicited. No signs of inherited syphilis were found. The patient expressed no communication with the outer world, could not feed herself, see or speak, but cried a good deal when handled.

Laboratory Tests Blood Red blood cells, 4,190,000, white blood cells, 8,500, Differential Polymorphonuclears, 64 per cent, small mononuclears, 28 per cent, large mononuclears, 7 per cent, eosinophils, 1 per cent

The Wassermann test was negative

The urine had a specific gravity of 1.008, was acid and contained a trace of albumin Fehling's was negative

The microscopic examination was negative

The cerebrospinal fluid under pressure of 120 mm was clear

The white cell count was 2 per cubic millimeter The Nonne, Noguchi and Fehling's tests were negative

The Wassermann test in the spinal fluid was negative The temperature varied between 97 and 100.5 The pulse ranged from 90 to 100



Fig 4—Patient D F, aged 4 years

Generalized convulsions occurred about every week and lasted from three to five minutes Twitchings, or rather tonic spasms of the quadriceps femoris, all the muscles of the shoulder girdle, arms, hands, and neck, developed and were continuous except during sleep The introduction of stovain (1/30 gr) into the subarachnoid space controlled the spasms for six hours Finally the spasms of the masseters became so severe that the lower jaw was dislocated Meantime dysphagia and marasmus became very marked, the temperature rose suddenly to 105 and the patient died, three years after the onset of the disease

The brain alone was permitted to be removed at necropsy, three hours after death, by Dr J Oliver, whose studies on the pathology of this case are detailed hereafter

The chief interest now centers itself about the etiology of this disease, which still is a matter of much discussion. Is the disease inherited or due to some inherent defect in the gray matter of the central nervous system, or, if acquired, is it due to some kind of degeneration? Pathologic studies alone can help us in this search.

Sachs thought the disease was due to "an arrest of cerebral development"—agenesis corticalis, as he called it. Others, including Kingdon,¹⁴ thought it an acquired disease, purely degenerative in character. Still others considered the changes due to certain toxins, syphilis or tuberculosis.

Sachs says "A child to be afflicted with amaurotic family idiocy is born with a limited and restricted capacity for normal development. Its gray cells may do as well as any other child's up to 2, 3 or 6 months, but beyond that its powers for further development will not go." Therefore, he considers this disease a *congenital affair* in which, when normal development ceases, degeneration begins.

Hirsch¹⁵ emphatically is determined that its character is acquired, caused by toxemia.

In the case cited above a family history pregnant with nervous disorders (some of which might have been similar to the disease under discussion), alcoholism soon after birth, and later food poisoning were prominent features. Could not this child have had a nervous system which was fertile soil for the production of this disease by disturbed metabolism with toxemia produced by alcohol and food poisoning? Dixon and Cohen¹⁶ have tried to unite the inherited, toxic and degenerative theories advanced, and this case seems an ideal one, not only to justify a suitable explanation for its etiology, but to knit more closely the two types of this disease into one, namely, amaurotic family idiocy.

PATHOLOGIC REPORT

Few nervous diseases have received the careful study that has been given to the pathologic anatomy of amaurotic family idiocy. Though a comparatively rare disease, we know the structural changes which characterize the process so definitely that we may consider them pathognomonic of the disease. It is with some hesitation, therefore, that a detailed description of a new phase is given. Certain more unusual appearances have been met, however, which merit attention, and for the sake of completeness the entire findings have been given.

The literature of the subject has grown to such enormous proportions since the appearance of Sachs' original description³ that a

14 Kingdon. Tr. Ophth. Soc. United Kingdom, 1892, xii.

15 Hirsch. Jour. Nerv. and Ment. Dis., 1898, xxv, p. 538.

16 Cohen and Dixon. Jour. Am. Med. Assn., 1907, xliii, 1751.

review of the subject is impractical. Among the pathologic studies Schaffer's,¹⁷ Vogt's,¹⁸ Spielmeyer's¹⁹ and Mott's²⁰ works are representative. We would, however, note the articles of Bielschowski,²¹ Frey²² and Schob,²³ who have paid particular attention to the changes in the cerebellum, as similar alterations were found in our case.

The necropsy was done by me two hours after death. The body was that of an extremely emaciated, fairly well-developed female child of apparently 7 years of age. There was a marked atrophy of the muscles of the extremities. The pupils were equal and dilated. No superficial enlargements of lymphatic glands were seen. The abdominal and thoracic cavities and their contents were negative, with the excep-

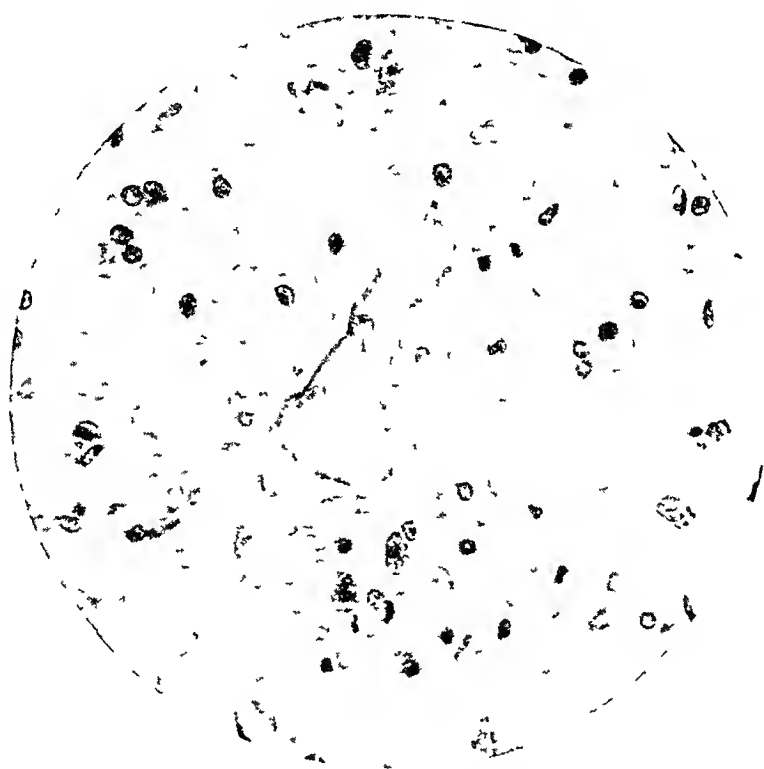


Fig 5—Precentral gyrus, Nissl stain. From photomicrograph. Two large pyramidal cells are seen with typical inflated areas. The nucleus of one is apparently normal. (Spencer 4 mm Obj. Compens. Oc. 9x)

tion of a bronchopneumonia in the lower lobes of both lungs. The head was well shaped, and the skull of normal thickness and contour. The dura was somewhat loose, apparently normal, there being no remains of any old trauma from the difficult labor. The pia showed

17 Schaffer. *Neurol Centralbl*, 1905, xxiv, 386-437.

18 Vogt. *Arch f Kinderheilk*, 1909, li, 1.

19 Spielmeyer. *Histol v Histopath Arbeit (Nissl)*, 11.

20 Mott. *Arch Neurol*, iii, 1907, 218.

21 Bielschowski. *Deutsch Ztschr f Nervenheilk*, 1913, i, 7.

22 Frey. *Virchow's Arch f path Anat*, 1913, ccxiii, 308.

23 Schob. *Ztschr f d ges Neurol v Psychiat, Orig*, 1912, x, 303.

a diffuse thickening over the anterior portions of the cerebrum, and over the base of the brain. The convolutions of the cerebrum were normal in arrangement, showing none of the abnormalities described by previous authors, such as, a communication of the rolandic with the sylvian fissure, a gaping of the opercula to show the insula, or irregularities in the anterior calcarine fissure. The gyri in the frontal regions were distinctly narrower than normal, and there was a consequent widening of the otherwise normal sulci. The hypophysis and large venous sinuses at the base of the skull were normal. The brain was hardened in 10 per cent formalin, and gross frontal sections made. In none of these was any abnormality in the white or gray matter noted.



Fig 6—Anterior horn cells of cervical cord, Nissl stain. From photomicrograph. One cell shows the "inflated area" and in the other a small amount of the tigroid substance still persists in the neighborhood of the nucleus (Spencer 4 mm. Obj. Compens. Oc. 9x).

For microscopic study sections were prepared from various regions and stained with the Weigert-Pal, Nissl, Bielschowski and Mallory's phosphotungstic hematoxylin methods.

Ganglion Cells—The ganglion cells of the central nervous system, whether motor or sensory, showed the same type of lesion. The changes were especially well marked in the precentral gyrus (Fig 5), the Purkinje cells of the cerebellum, the cells of the dentate nucleus and the anterior motor cells of the cervical cord (Fig 6).

The changes consist in a solution or disappearance of the Nissl substance with an accompanying distention of the cell body at this point, so that the term "inflated" has been applied to describe the appearance. The lighter staining degenerated area thus produced in the nerve cell is filled with a delicate reticulum. The nucleus is, as a rule, displaced to one extremity of the cell and often shows pyknosis, though it may retain an apparently normal structure (Fig 6). The disappearance of the tigroid substance begins in the neighborhood of the nucleus and extends gradually to the periphery of the cell (Fig 5).

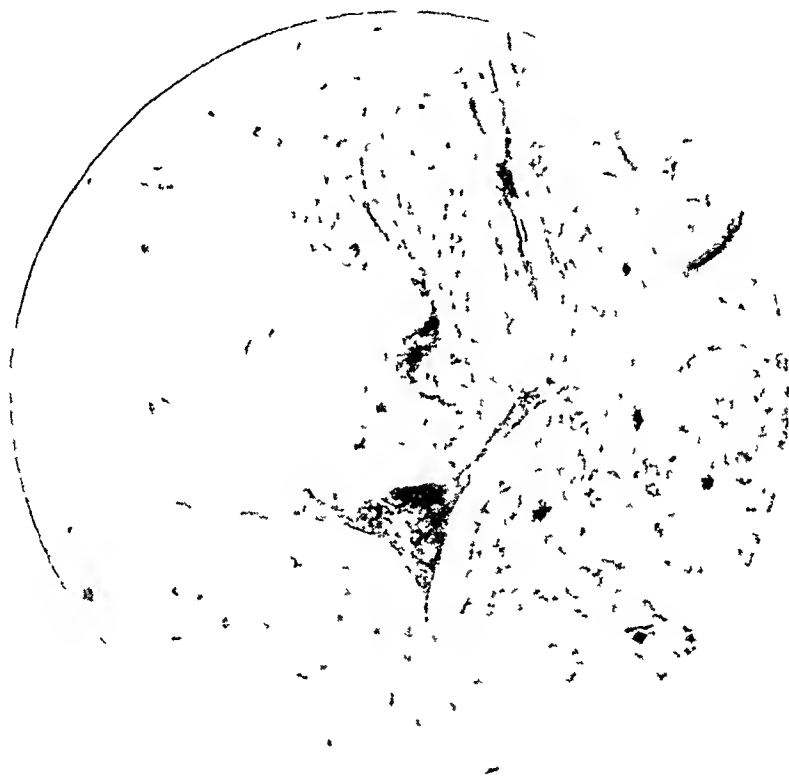


Fig 7—Purkinje cell of cerebellar cortex, Bielschowski silver impregnation. From photomicrograph. The upper part of the cell body is filled with deeply staining black granules. In the vertical dendrites are seen swollen areas filled with similar granules. (Spencer 4 mm Obj Compens Oc 9\)

The intracellular fibrils, as shown by the Bielschowski method, are entirely lacking in the "inflated" areas in the cell body, and persist only at the extreme periphery of the cell. The fibrillar structures of the dendrites and axons are as a rule normal.

The Sudan III preparations show the inflated areas of the affected cells to be filled with a fatty substance which stains a light orange-yellow. This lipid material is very finely divided so as to give a ground-glass appearance rather than of separate droplets.

Somewhat different appearances are seen in the Purkinje cells of the cerebellum. Here the characteristic inflation of the cell body with

displacement of the nucleus is seen, but the process extends as well into the dendrites. On these structures are seen irregular swellings sometimes as large as the cell body itself. The contents of these protuberances are either clear and resemble the "inflated" areas in the cell body, in which case they may be shown to contain a fatty material, or they are filled with densely packed, silver-reducing granules (Fig 7). Similar silver-reducing granules are seen in the cell bodies proper, and it would seem probable that they are of lipoidal nature. The axons, as far as they could be followed in the sections, were entirely normal.

The above described changes in the ganglion cells occurred with striking regularity throughout the entire central nervous system. There was, however, no marked decrease in the number of ganglion cells either in the cortex cerebri, in the Purkinje cells of the cerebellum or in the nucleoli of the brain stem. The arrangement of the layers of the cortex cerebri was still apparent, though somewhat indefinite on account of the marked degeneration of the constituent cells.

Medullated Fibers—The Weigert-Pal sections show little change in the medullated nerve fibers as compared with the widespread change in their cell bodies. Sections of the cerebral cortex show a slight scarcity of fibers in the tangential layers, but the radial fibers show little if any change. A similar preservation of the medullary fibers is found in the optic nerve, olfactory bulb and in the optic chiasma immediately posterior to the decussation. In the cervical cord a few degenerated fibers are found in the lateral columns in the region of the crossed pyramidal tracts.

Neuroglia—The neuroglia shows little evidence of proliferation in any of the regions examined. The greatest increase is found in the molecular layer of the cortex, especially in the frontal regions where the atrophy of the convolutions is most marked. Here a dense network of glia fibrils is seen, which is increased in thickness just below the pia.

Lipoids—The subject of the lipoids of the nervous system and their "Abbon" products is too extensive to be thoroughly considered in this brief report. A brief description of the more important findings will be given.

The more universal stains for lipoids, such as Sudan III or Scharlach R, give the best general picture of the state of these fatty substances in the diseased nervous systems. The "inflated" degenerated areas in the ganglion cells, as described above, are filled with a fine granular fatty substance which stains a light orange yellow.

Scattered among the medullated fibers are other cells which contain rather larger deeper orange staining droplets in varying numbers.

The number of such cells varies widely in different regions, being especially numerous in the cerebellum. They are most likely the glia cells described by many authors (Merzbach, Alzheimer) as *Abraumzellen*.

Still other cells filled even to a greater extent with intensely staining orange red droplets are seen grouped around the perivascular lymph spaces. These cells are crowded with droplets of all sizes, so that their nuclei are obscured. These are the "adventitial cells" of Marchand, or in some part the emigrated glia *Abraumzellen*.

By means of the various differential stains for fat a rough microchemical determination of the nature of the fat can be made. It is found that the lipoidal substance in the degenerated ganglion cells is related to the phosphorus containing phosphatids or lipins (Leathes) of which the so-called "lecithin" is an example. The simpler fats, such as neutral fatty esters and fatty acids, are found only in the adventitial cells surrounding the perivascular lymph spaces. The glia cells show an indefinite intermediate reaction which may be interpreted as a midstage in the breaking down of the more complex lipoids. A large number of these glia cells contain double refractive fats, which give the typical "Maltese cross" with crossed Nicol's prisms. A small amount of such doubly refractive fats is found in the adventitial cells. It would seem most likely that in these anisotropic lipoids we have to do with cholesterol esters or cholesterol mixtures.

The chemistry of the brain lipoids is one of the most complicated fields of the biochemical sciences, and as our knowledge of microchemical reactions is very incomplete, it is difficult to draw any definite conclusions as to the chemical changes which are progressing in these diseased nervous systems. We are, however, warranted in saying that there is a demonstrable breaking down of the complex lipoids (phosphorus and nitrogen-containing lipins) into their simpler components (neutral fats, fatty acids and cholesterol compounds) and that the glia and adventitial cells play an important part in this process. It is interesting to note that Mott and others have described an increase in the cholin content of the blood in cases of amaurotic idiocy, so offering a possible explanation of the removal of the phosphorus and nitrogenous constituents of the lipins (phosphatids).

It is unlikely that the above described changes in the lipoids are in any way characteristic of amaurotic idiocy, for similar processes would be expected in all affections of the nervous system in which degeneration of nervous elements plays an important rôle. A further study of various degenerative conditions is in progress and will be reported in greater detail at a later date.

Pathologically our case agrees in all essential details with the reports found in the literature. We would call especial attention to the fact that there is an equal agreement with the descriptions of the infantile type of the disease. Sachs²⁴ in speaking of this relation says, "While there is a superficial resemblance between the cell changes in these two varieties of amaurotic idiocy, the differences are still more striking. In the juvenile form the disease is not so universal as in the infantile and we fail to find the typical balloon-like enlargement of the cell bodies and the swelling of the dendrites so characteristic of the cells of the Tay-Sachs type." In the present case of the juvenile type we find all these changes mentioned by Sachs.

It is interesting to note a recent study of an infantile case by Savini-Castano and Savini²⁵ in which a very extensive discussion of the etiology, pathogenesis and pathologic anatomy is given, with a review of the literature to date. Their findings are in a sense a reversal to the original conception of Sachs, in that they describe a "Bildungshemmung" of the myelinated fibers. They therefore consider the condition a degenerative process which has affected an undeveloped nervous system. This last they assume from the lack of differentiation in the layers of the cerebral cortex, the lack of differentiation of the various regions of the cortex, and the failure of myelination of the nerve fibers.

The present case, however, furnishes further confirmation to the conception that the disease is a degenerative process affecting a nervous system lowered in resistance or in vitality. As we have no morphologic evidence of congenital abnormality, either gross or microscopic, it would seem that it is the lowered vitality which is transmitted at birth, and these cells of weakened resistance suffer at a later date from the effects of some toxic agent as yet unknown.

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Other contributions to the literature on this subject are the following:

Sachs, B. *Jour Nerv and Ment Dis*, 1892, *vi*, 603

Sachs, B. *Deutsch Med Wchnschr*, 1898, *xxiv*, 33

Jacobi. *Arch Pediat*, 1898, *xv*, 561

Holden. *Jour Nerv and Ment Dis*, 1898, *xxv*, 550

Clairborne. *Arch Pediat*, 1900, *x*, 3

Higier. *Deutsch Ztschr f Nervenheilk*, *xxxi*, 231

Higier. *Deutsch Ztschr f Nervenheilk*, *xxviii*, 388

Holmes, G. *Brain*, 1906, *xxix*, 180

Gifford. *Ophth Rec*, 1912, *xxi*, 577

Stewart. *Rev Neurol and Psychiat*, Edinburgh, 1912, *x*, 351

Smith, R. M. *Boston Med and Surg Jour*, 1912, *clxvi*, 376

Spiller. *Am Jour Med Sc*, 1905, *cxxix*, 40

²⁴ Sachs. *Jour Exper Med*, 1910, *xii*, 685

²⁵ Savini-Castano. *Ztschr f Kinderheilk, Orig*, 1913, *vii*, 321

STUDIES ON THE CIRCULATION IN MAN

XIII THE BLOOD FLOW IN THE HANDS AND FEET IN CERTAIN DISEASES OF THE NERVOUS SYSTEM ¹

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The study of the blood flow in the hands and feet is of special interest in diseases of the nervous system, in which the extremities are so often involved. The skeletal reflexes are so frequently affected that it seemed of some consequence to explore also the vasomotor reflexes by the method described in previous papers ¹. A preliminary account of some of the work was given in a Harvey Lecture ². The material available of course allowed a more complete study of some conditions than of others. Also, in a first survey, those conditions were naturally selected in which changes in the blood flow or in the vascular reflexes seemed most likely to be detected, and if detected to be capable of being most clearly related to the symptoms and morbid anatomy of the diseased states. Such conditions as affected only one side (hemiplegia, unilateral peripheral neuritis) were obviously of interest not only in connection with the pathologic physiology of the circulation, but also as affording the opportunity of testing still further the technic of the method, since they permitted the direct comparison of a normal part with the corresponding diseased part.

For one or other of these reasons it happens that most of the material studied in this paper falls under one of three heads. (1) Peripheral neuritis (due to trauma, rheumatism, alcohol, etc.), a case or two in which the condition was probably neuralgia rather than neuritis is included in this group, (2) cerebral hemorrhage (or obstruction of cerebral vessels) with hemiplegia, and (3) tabes. Some other cases are also introduced mainly for the sake of comparison. These comprise cases of motor neuron disease, cerebral tumor, and gunshot wound of the brain. Some observations, chiefly on the vascular reflexes, were made on patients affected by certain poisons which act especially on the nervous system (alcohol, lead), but in whom at the time of observation no symptoms of actual anatomic lesions (peripheral neuritis) were present. A case of excessive tobacco smoking and a

¹ Submitted for publication March 25, 1915

² From the H K Cushing Laboratory of Experimental Medicine, Western Reserve University

1 Paper II of this series, *Heart*, 1911, *iii*, 76, *Papers IX, X and XI, THE ARCHIVES INT MED*, 1913, *xii*, 678, *Ibid*, 1914, *xiii*, 1, 177

2 Nov 23, 1912

patient recovering from tetanus under treatment with antitoxin are also included because the vasomotor reflexes seemed to present points of interest. In one or two instances the blood-flow measurements were applied to the detection of malingering with, it is thought, helpful or at least suggestive results.

PERIPHERAL NEURITIS

In three cases of unilateral brachial neuritis, not of long standing, in which no decided atrophy of the hand had as yet occurred, although the strength of the grip was markedly diminished, the blood flow in the affected hand was conspicuously greater than in the contralateral normal hand. In two of these cases the lesion was on the right side and as has been mentioned in previous papers, normal right-handed persons usually show a slight preponderance in blood flow per 100 c c of hand volume on the right side. In the cases referred to, however, the difference was much greater, and one of the cases in which the lesion was on the left side presented an equally large excess in the left hand.

Thus in O A H, a man with right brachial neuritis probably of traumatic origin, and not at the time of observation associated with any wasting in the right hand, the flow in the right hand was 8.79 grams and in the left hand 6.99 grams per 100 c c of hand per minute, with room temperature 24 C. The ratio of the flows in the two hands (1.126) shows a very decided preponderance of flow in the affected hand.

O A H, a house carpenter aged 60, was admitted to the dispensary January 25, suffering from right brachial neuritis. Seven years ago he fell from a building on his right shoulder and has always had some pain in shoulder since. For three months he had severe pain and weakness in his shoulder. Pain is felt on pressure over the circumflex and over the median nerve above the elbow, and tenderness over the brachial plexus in neck and axilla. The grip of the right hand is much less strong than that of the left. Slight numbness is the only sensory disturbance. All movements of the right arm are weak, but there is no wasting of the hand. February 24. The systolic blood pressure is 130. No impairment of tactile sensation exists and warmth and cold sensibility is good. Pain sensation is diminished below the elbow. On April 26 his arm was better. The blood flow in the hands was examined January 12, before admission. Hands in bath at 3 p m, in calorimeters at 3.10 p m, removed from calorimeters at 3.26. 3,050 c c of water were in each calorimeter. Room temperature 24.1 C.

In Casimir M, a man aged 27, with left brachial neuritis, the blood flow in the right hand was 5.63 grams, and in the left hand 7.40 grams per 100 c c per minute, with an average room temperature of 21.9 C. The ratios of the flows in the two hands is 1.131, indicating a great excess in favor of the left hand. The case may fairly be considered an "early" one. Although there was some wasting of the muscles of the left upper arm, and some weakening of the grasp of the left hand,

little if any wasting of the hand as revealed by the volume measurement could be detected

TABLE 1—CALORIMETRIC MEASUREMENTS IN CASE OF O A H

Time	Right	Left	Time	Right	Left
3 00	29 98	29 87	3 21	30 43	30 18
3 12	30 00	29 89	3 22	30 50	30 25
3 13	30 03	29 91	3 23	30 57	30 30
3 14	30 09	29 94	3 24	30 63	30 36
3 15	30 13	29 97	3 25	30 71	30 41
3 16	30 20	30 01	3 26	30 78	30 48
3 17	30 23	30 02	3 35	30 68	30 40
3 19	30 32	30 10	3 51	30 52	30 26
3 20	30 38	30 13			

Cooling of calorimeters in twenty-five minutes, R, 0.26 C, L, 0.22 C. Volume of right hand in calorimeter, 445 cc of left 425 cc. Pulse 80*. Mouth temperature 37.1 C. Room temperature 23.9. He is right handed†.

* Except when otherwise mentioned the pulse rate was always taken in a sitting position.

† It is to be assumed that a patient is right handed unless the contrary is stated.

Casimir M. was admitted to the dispensary, January 4, with left brachial neuritis. He had noticed pain in the left elbow for three months, mostly when at work (as a sewing machine operator). He had had no injury. No local signs were seen at elbow. There was no history of venereal infection. Considerable thickening of the radial artery existed. On January 31 the left arm was still weak and he could not use it properly at work, while there was distinct atrophy of some of its muscles. The circumference of the left upper arm was 24.5 cm, that of right upper arm 26.5 cm, of left forearm 25 cm, and of right 26 cm. Pain on pressure was felt over some of the cervical nerves on the left side, but no pain on pressure over the arm. The grasp of the left hand was weaker than that of the right. On February 17 he felt much better. The blood flow in the hands was examined January 31.

The hands were put into the bath at 3.38½ p. m., into the calorimeters at 3.51, taken out of calorimeters at 4.08. 3,050 cc of water were in each calorimeter. Pulse 68. Mouth temperature 36.6 C.

TABLE 2—CALORIMETRIC MEASUREMENTS IN CASE OF CASIMIR M.

Time	Right	Left	Room	Time	Right	Left	Room
3 50	29 40	29 36	21.7	4 01	29 53	29 58	21.9
3 52	29 39	29 35		4 02	29 61	29 62	
3 54	29 42	29 41		4 03	29 64	29 65	
3 55	29 44	29 42		4 04	29 68	29 71	
3 56	29 45	29 43	22.1	4 05	29 71	29 75	
3 57	29 47	29 43		4 06	29 76	29 81	
3 58	29 49	29 48		4 07	29 78	29 83	
3 59	29 52	29 51		4 08	29 80	29 86	
4 00	29 55	29 53		4 27	29 56	29 63	

Cooling of calorimeters in nineteen minutes, R, 0.24 C, L, 0.23 C. Volume of right hand 400 cc, of left hand 370 cc.

In John S., a man with right brachial neuritis and distinct weakening although no definite wasting of the right hand, the flows were 10.29 grams and 7.66 grams per 100 cc per minute in the right and

left hands respectively, with room temperature 22.3 C. The ratio of the flows (1.134) denotes a great preponderance of flow in the hand affected by the lesion. On immersion of the left hand in cold water the flow in the right sank to 5.18 grams per 100 c.c. per minute for the first four minutes and then rose to 8.16 grams per 100 c.c. per minute for the remaining five minutes of the period of immersion. On immersing the left hand in warm water the flow in the right hand mounted to 10.16 grams, which was scarcely equal to the initial flow. This indicates that the flow in the right hand at the beginning of the observation was probably already associated with a considerable vasodilatation on which it was easy to impose a decided reflex vasoconstriction but not an additional vasodilatation.

John S., a bricklayer aged 45, was admitted to the dispensary on February 27 with neuritis in the right arm. He had had pain in right elbow for four weeks, unaccompanied by heat or swelling, and the arm had lost strength. The grip of the right hand was much weaker than that of the left. Tenderness was felt over the external condyle, and very slight tenderness over the right brachial plexus. He attributed the condition to cold. March 6, his condition was the same. The blood flow in the hands was examined February 27.

The hands were put into the bath at 2.50 p.m., into the calorimeters^{*} at 3, removed from calorimeters at 3.37. At 3.15 the left hand was immersed in water at 9 C., and at 3.24 in water at 43 C. At 3.31 the left hand was dried and wrapped up. Pulse 74. Mouth temperature 36.74 C.

TABLE 3—CALORIMETRIC MEASUREMENTS IN CASE OF JOHN S.

Time	Right	Left	Room	Time	Right	Left	Room
2.59½	29.61	29.50		3.20	30.77		
3.02	29.69	29.55	23.3	3.21	30.61		
3.03	29.72	29.59		3.22	30.66		
3.04	29.78	29.63		3.23	30.69		
3.05	29.84	29.67		3.24	30.73		
3.06	29.90	29.71		3.25	30.77		23.3
3.07	29.96	29.75		3.26	30.81		
3.08	30.02	29.83	23.4	3.27	30.87		
3.09	30.09	29.88		3.28	30.91		
3.10	30.16	29.92		3.29	30.97		
3.11	30.21	29.96		3.30	31.02		
3.12	30.28	30.03		3.31	31.08		
3.13	30.33	30.06		3.32	31.11		
3.14	30.39	30.11	22.8	3.33	31.14		
3.15	30.45	30.15		3.34	31.19		22.9
3.16	30.48			3.35	31.23		
3.17	30.50		23.3	3.36	31.27		
3.18	30.52			3.37	31.30		
3.19	30.53			3.43	31.22	29.91	

Volume of right hand 412 c.c., of left hand 402 c.c. Cooling of calorimeters, R, 0.08 C. in six minutes, L, 0.24 C. in twenty-eight minutes.

The most natural explanation of the preponderance in the flow on the side of the lesion is that the vasoconstrictor fibers are involved in the neuritis, with a resultant diminution of the vasomotor tone of the hand. It is difficult to see how a neuritis due to trauma or to pressure

^{*} As always, unless otherwise stated, the quantity of water in each hand calorimeter was 3,015 c.c.

could fail to affect these fibers. Nor is there any evidence that they escape completely in other forms of peripheral neuritis although, until it is eliminated by proof to the contrary, the possibility must be granted that a particular poison may spare the efficient vasomotor fibers in the peripheral nerves which it attacks. In a peripheral neuritis involving the vasoconstrictors these need not of course be totally incapable of conduction any more than the motor fibers of the part. In the case of John S., for example, it is evident they were not completely paralyzed, since a good reflex vasoconstriction was obtained when the contralateral hand was put into cold water. There is some indication, however, that such a reflex, even when of as great an initial intensity as normal, may be more fleeting than under normal conditions, perhaps because the partially degenerated fibers or their endings are sooner fatigued.

In a fourth case, that of Kaspar J., a man suffering from "early" unilateral brachial neuritis apparently of rheumatic origin, a similar disproportion between the flows in the two hands was noticed, the preponderance being, as before, in favor of the affected hand. Later on, however, in this case practical equality in the flows in the two hands was observed, either because the improvement in the condition had progressed so far at the second examination that the vasomotor tone of the affected hand had again become normal, or possibly because of the action of the salicylates with which he was being treated. At the first examination the flow in the hand on the side of the neuritis (the right) was 4.80 grams per 100 c.c. per minute (allowing for the swelling of the hand) and in the left 3.58 grams, the ratio being 1.134, with room temperature 24.2 C. These flows are subnormal, which may of course be due to the man's general condition, recovering as he was from an acute illness (rheumatic fever). The heart was probably to some extent handicapped. Also arteriosclerosis was present, which is always associated with a subnormal hand flow³.

At the second examination with a somewhat higher room temperature (25.3 C.) the flow was practically the same in the left hand (3.72 grams) but in the right hand it was reduced almost to equality with that in the left (3.76 grams per 100 c.c. per minute). The fact that the flow in the left hand remained so low in spite of the relatively high room temperature seems to indicate a great tendency to vasoconstriction. If this were the case we should expect that the preponderance of flow previously observed in the right hand, which by hypothesis was due to diminution, though not to paralysis, of vasoconstrictor tone, should tend to disappear. The slight tendency to vasodilatation is indicated clearly by the tests of the vasomotor reflexes. During immer-

3 Paper XI of this series, *THE ARCHIVES INT. MED.*, 1914, LIII, 177

sion of the left hand in warm water the flow in the right sank to 2.68 grams per 100 c c per minute for the first four minutes of immersion and only reached 4.12 grams per 100 c c per minute for the remaining seven minutes. For the first three minutes of immersion of the left hand in cold water the flow in the right was 2.74 grams and for the remaining six minutes 3.75 grams per 100 c c per minute. The marked slowing of the pulse rate (57 per minute as compared with 92 at the previous examination), in spite of the higher room temperature and the unchanged body temperature, may be associated with the tendency to peripheral vasoconstriction.

Kaspar J, a laborer aged 50, was admitted to Lakeside Hospital, April 12, with rheumatic fever. Two weeks before, he began to have severe pain in the left ankle and knee, later in the right knee. Five days before admission the right elbow, wrist, and later the shoulder began to trouble him. The heart sounds were clear, the pulse regular in rate, but irregular in amplitude. The vessel wall was palpable. On April 20 the legs were well, but the right upper arm was still sensitive and much atrophied. On April 30 there was very little pain, but movement of the right arm was much impaired, analgesia existed over the entire right arm. The blood flow in the hands was examined May 5 and again May 8. The grip of the right hand was still weak, pain was felt over the right brachial plexus. Convalescence was uninterrupted and he was discharged May 12.

The hands were put into the bath at 2:36½ p m, into the calorimeters at 2:46½. At 2:56½ the left hand was put into water at 43° C. At 3:04 the left hand was put into water at 9.5° C. He felt the cold water painful. At 3:13 the right hand was removed from the calorimeter. Pulse 92. Mouth temperature 36.7.

TABLE 4—FIRST BLOOD FLOW EXAMINATION OF KASPER J

Time	Right	Left	Room	Time	Right	Left	Room
2 45	29 65	29 56		3 02	30 09.5		24 25
2 48	29 67	29 57		3 03	30 13		
2 49	29 69	29 60		3 04	30 17.5		
2 50	29 71	29 62		3 05	30 20		24 4
2 51	29 75	29 63		3 06	30 21.5		
2 52	29 78	29 64		3 07	30 24		
2 53	29 80	29 67		3 08	30 28		
2 54	29 84	29 70		3 09	30 31		
2 55	29 88	29 72	24 2	3 10	30 34		24 4
2 56	29 90	29 74		3 11	30 37		
2 57	29 93	29 76		3 12	30 40		
2 58	29 96.5			3 13	30 44		
2 59	29 95		24 2	3 21		29 57	
3 00	30 03			3 22	30 34		
3 01	30 07						

Volume of right hand 511 c c, of left 457 c c. The right hand is still somewhat swollen and noticeably larger than the left. Cooling of calorimeters, R, 0.10° C in nine minutes, L, 0.19° C in twenty-four minutes.

The particulars of the second examination of Kaspar J are given in the general table.

In a fifth case (John McH.), although symptoms described by the patient suggested a right brachial neuritis, the suspicion of malingering could not be excluded. The flow in the right hand was 4.30 grams

and in the left 391 grams per 100 c c per minute with room temperature at 23.3 C. The ratio of the flow of the two hands is 1.11. On the following day another examination was made and the flows came out 546 grams and 474 grams for the right and left hands respectively with the same room temperature, a ratio of 1.15. Immersion of the left hand in warm water caused a marked vasoconstriction in the right hand for the first six minutes, reducing the flow to 323 grams per 100 c c per minute. This was succeeded by a moderate vasodilatation (for the remaining seven minutes of the period of immersion of the left hand) the flow in the right hand increasing to 611 grams.

John McH., a laborer, aged 58, was admitted to the City Hospital, June 4, apparently suffering from right brachial neuritis. He complained of stinging and numbness of right forearm and hand, especially the middle finger. He had been addicted to alcohol and had several attacks of delirium tremens. There was pain on pressure over the right shoulder, at the inner side and front of the head of the humerus. He could raise his right arm slowly and apparently with some pain to the horizontal position but not higher. His hands felt cold. He said he was cold all over. He stated that he sometimes had sudden swelling of the back of the right hand, which disappeared in a few minutes. He had no trouble in walking but said he was "very irritable and twitched a great deal." There seemed to be a considerable mental factor in the case and a possibility of malingering. The pain and tingling did not inconvenience him, but he feared they might be premonitory of a "stroke." Blood flow in hands was examined on June 5 and again on June 6. Particulars of the first blood-flow examination are given in the general table.

TABLE 5—CALORIMETRIC MEASUREMENTS IN SECOND EXAMINATION OF JOHN McH

Time	Right	Left	Room	Time	Right	Left	Room
2 40	31 40	31 31		3 00	31 80	31 66	
2 42	31 39	31 31		3 01	31 835	31 695	
2 43	31 40	31 32		3 02	31 85	31 71	23 15
2 44	31 41	31 33	23 1	3 03	31 88	31 72	
2 45	31 425	31 35		3 04	31 88		22 9
2 46	31 46	31 375		3 05	31 89		
2 47	31 49	31 41	23 1	3 06	31 90		
2 48	31 52	31 425		3 07	31 91		
2 49	31 54	31 44	23 2	3 08	31 925		22 9
2 50	31 575	31 46		3 09	31 935		
2 51	31 59	31 48		3 10	31 965		
2 52	31 60	31 49	23 2	3 11	31 99		23 05
2 53	31 625	31 52		3 12	32 02		
2 54	31 66	31 54		3 13	32 045		
2 55	31 68	31 55	23 4	3 14	32 075		
2 56	31 71	31 58		3 15	32 09		23 0
2 57	31 75	31 625		3 16	32 12		
2 58*	31 78	31 635	23 2	3 39	31 82	31 29	
2 59	31 795	31 65					

Cooling of calorimeters, R, 0.30 C in twenty-three minutes, L, 0.43 C in thirty-six minutes. Rectal temperature 37.5 C. Volume of right hand 512 c c, of left 491 c c. Water equivalent of calorimeters with contents, R, 3,504, L, 3,488. Blood pressure left arm, systolic 116, 93 (sound gone). Right arm, 115, 93.

* Here he heard warm water ordered and became anxious.

At the second examination the patient says the pain in the right shoulder is rather worse than yesterday. The hands were placed in bath at 2 32 p m, in the calorimeters at 2 41½, taken out of calorimeters at 3 16. Pulse 88. At 3 03 left hand was put into water at 43 C.

While it would of course be absurd to claim that such observations would of themselves be sufficient to justify a diagnosis of malingering in this case the slight difference in the flows in the two hands, scarcely exceeding if at all that often observed in normal persons, suggested that if the symptoms described were genuine they were due rather to a functional than to a structural lesion—to a brachial neuralgia rather than to an "early" brachial neuritis. In the period during which the patient was still under observation the condition did not develop further and he was discharged "improved" a very few days after the last examination. There is little doubt that in cases in which certain neurologic conditions are simulated a measurement of the blood flow might sometimes help to clear up the diagnosis. In long-standing paralyses whether due to a peripheral or to a central lesion there is a decided diminution in the blood flow of the affected hand (or foot) as compared with the normal part.

Thus, in a case of long-standing brachial neuritis of the right side associated with cervical rib (Mrs M C) the flow was much smaller in the affected than in the normal hand (3 98 grams per 100 c c per minute in the right, and 5 70 grams in the left hand) the ratio being 1 1 43, with room temperature 23 5 C). This agreed with the statement of the patient that the right hand was always colder than the left. There was slight wasting of the right hand, only clearly revealed by measurement of the volume, but the hand was little used. The atrophy chiefly affected the proximal segments of the limb. Here it may be supposed that the nerve lesion has led to anatomic changes in the blood vessels causing a narrowing of their lumen.⁴

Mrs M C, aged 38, was admitted to the dispensary in April, 1910. She states that in her fourteenth year she worked very hard in a hayfield on a hot day, had sunstroke and fell unconscious. When she recovered consciousness, right arm and shoulder were aching and there was some loss of power there. This has gone on gradually increasing. Continuous pains have been in the right shoulder for the past three weeks. There is exostosis of the scapula (curved scapula) and a marked prominence in right supraclavicular region extending upward and forward for two inches and pressing on the brachial plexus. Cervical ribs were shown by Roentgen ray. Extreme tenderness was felt on pressure in supraclavicular region. Atrophy and weakness were noted of the serratus magnus, infraspinatus, supraspinatus, and latissimus dorsi. The deltoid and other muscles of the arm and forearm show weakness and slight atrophy. There was no apparent wasting of the right forearm or hand, although she does not now use them much. The grip of the right hand was fairly strong, although weaker than the left. She was right handed. There

⁴ Todd Jour Nerv and Ment Dis, 1913, xl, 439

was a marked diminution of sensation to pricking and to contact with camel's hair brush over right shoulder. Over arm and forearm sensation is normal. Blood flow in hands was examined Feb 14, 1911.

Hands in bath at 2 03 p m, were placed in calorimeters at 3 14, and taken out of calorimeters at 3 29. Pulse 88. Mouth temperature 37.4 C. Room temperature 23.8 C.

TABLE 6—CALORIMETRIC MEASUREMENTS IN CASE OF MRS. M. C.

Time	Right	Left	Time	Right	Left
3 13	30 29	30 27	3 23	30 38	30 46
3 16	30 27	30 27	3 24	30 39	30 48
3 17	30 29	30 31	3 25	30 40	30 50
3 18	30 30	30 33	3 26	30 41	30 51
3 19	30 31	30 34	3 27	30 42	30 52
3 20	30 33	30 38	3 28	30 43	30 55
3 21	30 35	30 41	3 29	30 44	30 57
3 22	30 36	30 43	3 54	30 21	30 34

Cooling of the calorimeters in twenty-five minutes, 0.23 C. Volume of right hand 295 c.c., of left hand 301 c.c.

The possibility of distinguishing a neuralgia from an "early" neuritis by measurement of the blood flow seems to be indicated by such cases as that of Max B., a carpenter, aged 24, in whom the diagnosis of occupational neuralgia (possibly with slight neuritis) was made.

The blood flow came out 13.89 grams per 100 c.c. per minute for the right (the affected) hand and 13.38 grams for the left, with room temperature 24.5 C. (ratio of flows in the two hands 1.104). These flows are of a normal order of magnitude for the age and general condition of the patient and the room temperature. The slight preponderance of flow in the right hand is no more than that usually observed in normal right-handed persons. If the condition were a typical "early" neuritis a much greater excess of flow in the affected hand would be expected, owing to paralysis of vasoconstrictors. The vasoconstrictor reflex in the right hand when the left was immersed in cold water was well marked, the flow falling to 7.25 grams for the first three minutes of immersion, but rising again during the remaining six minutes to 10.83 grams per 100 c.c. per minute. Immersion of the left hand in warm water caused a moderate increase in flow in the right (to 12.53 grams per 100 c.c. per minute for the whole period of immersion of seven minutes). The initial value was not reached. The vasomotor reflex to warmth in this experiment differed from that in normal cases and also from that in the cases of undoubted neuritis in this respect, that there was no distinct initial diminution of flow in the right hand when the left was put into the warm water, or a very slight and transient one. There is not enough material, however, to show whether this has any general significance. The protocol of the case has already been published.⁵

⁵ Cleveland Med. Jour., 1911, x, 398.

One case diagnosed as sciatica of the left leg was examined

Frank S, a man aged 64, a laborer in a stable, had to sleep about the stable, often on the wet floor. For six weeks previous to admission the leg had been growing rapidly worse. Now he can hardly bear his weight on it. The trouble is worse at night. Both knee-jerks are exaggerated, especially the left. The Achilles jerk is evident on the left side. Some tenderness is present along the nerve trunks of the left leg, which feels cold at times.

At the first examination of the blood flow—three days after admission when the condition was still acute—the flow in the feet was found exceedingly small both absolutely and in proportion to the hand flow, namely, 0.22 gram per 100 c.c. per minute for the right foot, and 0.47 gram for the left, with room temperature 21 C. Immersion of the right foot in warm water caused no increase in the flow in the left foot, which for ten minutes during immersion of the right foot continued at the rate of 0.43 gram per 100 c.c. per minute. The flow in the right hand was 4.20 grams, in the left 4.39 grams, with room temperature 22.1 C. The ratio of the combined foot flows to the combined hand flows was 1:12.4, indicating a marked tendency to vasoconstriction in the feet, possibly due in part to the pain. The fact that in spite of this tendency to vasoconstriction the flow in the left foot is double that in the right would seem to indicate a condition of the nerves of the left leg constituting a partial block for vasoconstrictor impulses. If a condition of neuritis of the large nerve trunks of the leg is present this would agree with the results on cases of brachial neuritis. Twenty-two days later, when the pain in the thigh had disappeared, the flow in the left foot was found somewhat inferior to that in the right, which agreed with the fact that for three or four days previous to the examination he had felt the left foot cold, although it was covered with sweat.

A number of cases of alcoholic neuritis came under observation. A detailed account of the results in one will suffice. A second case is considered in another connection in Paper XII, published in *Journal of Experimental Medicine*, xxii, 1915, No. 1.

Charles de M., a pianist, aged 29, height 6 feet, 1 inch, weight 170 pounds, was admitted to the City Hospital, July 9, with diagnosis of chronic alcoholism with neuritis. He has been drinking since boyhood and drinks a quart of whisky daily. There is no noticeable anemia. The heart and lungs are normal. The liver is palpable. Knee-jerk and tendo Achillis reflex are markedly exaggerated. A musculo-spiral paralysis of the left forearm and wrist with well-marked wrist drop is present. There is tenderness but no atrophy. The left hand is weaker than right, the left foot is also worse than the right. Two months ago there was marked toe-drop in the left foot. He could stand on the right foot alone but not on the left. The toe-drop is not now so bad. A general tremor exists. The maximum temperature on July 11 was 100.6 F. After this it was never above 99.6 F. with a minimum of 97.8 F. The patient sweats freely. He was discharged improved, July 29. The blood flow in the hands

was examined on July 10 and in the feet and hands on July 16 He was unable to walk into the room

First examination, July 10 Hands in bath at 1 58½ p m, in calorimeters at 2 08½ At 2 25 the right hand was put into water at 81 C, and at 2 35 into water at 43.1 C He complained much of the cold water At 2 44 the right hand was taken from the calorimeter Pulse 68 The day was very warm

TABLE 7—CALORIMETRIC MEASUREMENTS IN CASE OF CHARLES DE M

Time	Right	Left	Room	Time	Right	Left	Room
2 07	31 325	31 32	30 1	2 27		32 425	
2 09½	31 37	31 36		2 28		32 45	
2 10	31 39	31 39		2 29		32 49	
2 11	31 46	31 45	30 2	2 30		32 55	29 9
2 12	31 505	31 525		2 31		32 60	
2 13	31 57	31 60		2 32		32 64	
2 14	31 63	31 68		2 33		32 695	
2 15	31 685	31 75		2 34		32 73	29 8
2 16	31 75	31 81	30 1	2 35		32 77	
2 17	31 81	31 86		2 36		32 815	
2 18	31 87	31 93		2 37		32 85	
2 19	31 94	32 01		2 38		32 90	29 8
2 20	32 00	32 05		2 39		32 945	
2 21	32 065	32 125	30 0	2 40		32 995	
2 22	32 125	32 18		2 41		33 04	
2 23	32 19	32 26		2 42		33 10	
2 24	32 26	32 32		2 43		33 14	
2 25	32 31	32 365	30 0	2 44		33 20	29 7
2 26½		32 42		2 50	32 17	33 11	

Cooling of calorimeters, R, 0.14 C in thirty-four minutes, L, 0.09 C in fifteen minutes Volume of right hand 488 cc, of left hand 479 cc Rectal temperature 37.5 C Water equivalent of calorimeters with contents, R, 3,485, L, 3,478 Blood pressure left arm, systolic 118 (palpation), 121 (stethoscope), 74 (sound gone)

Second examination, July 16 The patient's left hand is to-day in a splint on account of wrist-drop It feels stiff and swollen, probably from the pressure of the splint He walked into the room without help and feels much better Hands in bath at 3 07 p m, were in calorimeters at 3 17, and out of calorimeters at 3 29 Pulse 84 The weather is much colder than at the last examination

TABLE 8—CALORIMETRIC MEASUREMENTS IN SECOND EXAMINATION OF CHARLES DE M

Time	Right	Left	Room	Time	Right	Left	Room
3 15	31 40	31 39	24 9	3 25	31 83	31 77	
3 18	31 425	31 405	25 2	3 26	31 90	31 805	25 1
3 19	31 495	31 465		3 27	31 95	31 855	
3 20	31 56	31 51	25 15	3 28	31 99	31 89	
3 22	31 66	31 60		3 29	31 035	31 935	
3 23	31 72	31 66		3 35	31 96	31 86	
3 24	31 79	31 71					

Cooling of calorimeters in six minutes, R, 0.075 C, L, 0.075 C Volume of right hand 479 cc, of left hand 494 cc Water equivalent of calorimeters with contents, R, 3,478, L, 3,490 Rectal temperature 37.7 C

At the first examination in Charles de M the flow in the right hand was 9.96 grams per 100 cc per minute, in the left (the weaker of the two hands) 10.76 grams, with the very high room temperature 30.1 C The ratio between the flows in the two hands was 1.108 These flows

are subnormal for his age at this room temperature. Immersion of the right hand in cold water caused a good reflex vasoconstriction, the flow in the left dropping to 5.84 grams per 100 c.c. per minute for the first three minutes, to rise again to 9.45 grams per 100 c.c. per minute for the next seven minutes of the immersion. Immersion of the right hand in warm water caused only a very moderate increase above the initial flow in the left hand (to 11.27 grams).

At the second examination, six days later, the flow was 9.92 grams for the right hand and 8.95 grams for the left with room temperature 25.1 C. These flows are fairly normal for the room temperature, and the patient's condition was much better than at the previous examination. His pulse rate was 84 instead of 68. The deficiency in the flow in the left hand is probably to be attributed to obstruction caused by a splint. But in no patient with alcoholic neuritis examined has the same marked difference between the two hands (or feet) been observed as in the cases of brachial neuritis already described. Two points have to be considered in this relation—first, in alcoholic neuritis the action of the poison is necessarily bilateral, although the neuritis may at a particular time have progressed farther on the one side than on the other. Secondly, if, as appears often to be the case, it is the small muscular branches which are specially affected in alcoholic neuritis, a very marked increase in the blood flow of the hand most affected by the neuritis could scarcely be expected, since the hand flow is above all a cutaneous blood flow.

The flow in the feet at the second examination of Charles de M. came out 0.90 gram per 100 c.c. per minute for the right foot and 1.20 grams for the left. These flows are not only absolutely small, but small in proportion to the hand flows. The preponderance is on the side (left) on which the foot-drop is worse, but in dealing with such small flows, particularly in the case of the feet in which vasoconstriction caused by the necessary manipulations connected with the measurement is not easily avoided in patients specially susceptible to this condition, too much stress must not be laid on small differences. The next case, although the patient was much addicted to alcohol, probably represents a neuritis due to pressure.

Frank D., aged 39, height 5 feet, 11 inches, a school teacher in Germany, since then a casual laborer, was admitted to the City Hospital, July 22, with wrist-drop of left hand. Pronation and supination are perfect. He can palmar-flex left hand to some extent but cannot dorsiflex it. He has long been a heavy drinker and has had delirium tremens. Has been sleeping outside. On the morning of July 21 he first noticed that he could not move his left hand. For all he knows he may have been lying on it. He never had anything of the kind before. Some numbness is present on the dorsum of the left hand, especially on the radial side, although pin pricks and contact of the blunt point are felt everywhere. Wrist-jerk is absent on the left side, but is well marked on the right. Knee-jerk is present on both sides. The heart and lungs are normal.

There is no noticeable anemia. He was discharged improved July 27. The blood flow in the hands was examined July 23.

The hands in bath at 1 54 p m, were in calorimeters at 2 06. Left hand out of calorimeter at 2 47. The right hand was put into cold water (8 C) at 2 23 p m. Pulse 76. At 2 34 right hand was put into water at 43 C.

TABLE 9—CALORIMETRIC MEASUREMENTS IN CASE OF FRANK D

Time	Right	Left	Room	Time	Right	Left	Room
2 05	31 01	30 97		2 28		32 075	25 1
2 07	31 025	30 985		2 29		32 13	
2 08	31 06	31 01		2 30		32 17	25 05
2 09	31 095	31 05	25 1	2 31		32 24	
2 10	31 14	31 08		2 32		32 28	
2 11	31 19	31 11	25 2	2 33		32 325	
2 12	31 235	31 165		2 34		32 35	25 15
2 13	31 30	31 23		2 35		32 365	
2 14	31 38	31 29		2 36		32 37	
2 15	31 43	31 36	25 2	2 37		32 38	
2 16	31 505	31 43		2 38		32 395	25 25
2 17	31 57	31 49		2 39		32 405	
2 18	31 635	31 565		2 40		32 45	
2 19	31 70	31 635		2 41		32 50	
2 20	31 78	31 72		2 42		32 56	
2 21	31 84	31 79	25 2	2 43		32 61	
2 22	31 91	31 86		2 44		32 665	25 2
2 23	31 95	31 94		2 45		32 72	
2 24		31 97		2 46		32 78	
2 25		31 995		2 47		32 845	
2 26		32 01		3 06	31 53	32 62	
2 27		32 05					

Cooling of calorimeters, R, 0.46 C in forty-three minutes, L, 0.225 C in nineteen minutes. Volume of right hand, 572 c c, of left hand 542 c c. Water equivalent of calorimeters with contents, R, 3,553, L, 3,529. Rectal temperature 37.6 C. Blood pressure left arm systolic 133 (palpation), 133 (stethoscope), 86 (sound gone). Another observation 133, 87.

In the case of Frank D a slight preponderance of flow in the left hand was observed, 10.18 grams per 100 c c per minute for the right hand and 10.54 grams for the left with room temperature 25.2 C for the last 11 minutes before testing the vasomotor reaction. The ratio of the flows in the two hands is 1.103. Immersion of the hand in cold water caused a good and durable vasoconstriction in the left hand. Immersion of the right hand in warm water occasioned a great initial vasoconstriction in the left, lasting for three minutes, during which the flow was reduced to 3.38 grams per 100 c c per minute. This gave way suddenly, as is normally the case, to vasodilatation, the flow in the left hand reaching 10.81 grams per 100 c c per minute for the remaining eight minutes of immersion of the right in the warm water. It will be observed that the initial flow was only slightly surpassed.

Since in this case the paralysis is confined to one hand, no other part of the body being at all affected, and since it came on suddenly, the conclusion seems justified that it was a pressure palsy. It is known that the long supinator sometimes escapes in pressure paralysis of the musculo-spiral nerve. Obviously cutaneous nerves are only slightly involved, and vasomotor fibers for the cutaneous vessels would not in

this case be affected to any appreciable extent. Moreover it has been stated that the radial nerve does not carry vasomotor fibers⁶

Although this statement is probably based on too slight an experimental foundation and need not be taken literally, it is clear enough that in the case under consideration a difference in the flow in the two hands comparable to that observed in lesions affecting the brachial plexus could not be expected.

In a case of motor neuron disease without sensory deficiency (Mrs Mary N) the vasoconstrictor reflexes were found to be of quite normal intensity and of more than normal duration.

Mrs Mary N, a tailoress, height 5 feet, 6 inches, aged 46, was admitted to the dispensary, Nov 10, 1910, suffering from progressive muscular atrophy. Her left hand became very painful about September, 1909. About a month thereafter she noticed some atrophy of the thenar eminence and weakness of the hand. About Christmas, 1909, the right hand became similarly affected. The condition gradually progressed and now the right arm shows some atrophy of the deltoid and musculo-spiral paralysis in the forearm, and wrist-drop with some median paralysis as well. Some atrophy of the thenar eminence exists. On the left side there is atrophy of the thenar eminence and some weakness of flexors and extensors but no wrist-drop. No loss of reflexes is shown in either arm. Both wrists and hands are wasted. The grip of both hands is very weak. The left leg is smaller than right, and has been so, at any rate, from the age of 3. It shows peroneal palsy with foot-drop and shortened Achilles tendon, yet she can walk well. Some pain is present along the spine at the base of the neck. Knee-jerk and Achilles reflex are exaggerated on the right side, absent on the left. Babinski's sign is noted in the left foot. There is no sensory disturbance, clonus, or Romberg's sign. The pupils react to light and accommodation. The blood gives a strongly positive Wassermann reaction. The spinal fluid shows 150 cells per c c, practically all mononuclear. The Noguchi reaction is positive. Physical examination of thorax is negative. Treatment with mercurials and potassium iodid, also with salvarsan, was without result. The patient continued to come to the dispensary till January, 1913, her condition gradually growing worse.

On March 7, 1912, the blood flow in the hands was examined. Hands in bath at 2 27½ p m, in calorimeters at 2 38. At 2 52 the right hand was put into water at 8 C. At 3 p m right hand was put into water at 43 C, which caused the hand to tingle. At 3 07 right hand was dried and wrapped in warm cloth. At 3 14 right hand was removed from calorimeter. Pulse 116. Mouth temperature 37.6 C.

The blood flow in the right hand was 6.99 grams, and in the left 7.13 grams per 100 c c per minute with room temperature 23.6 C. Immersion of the right hand in cold water caused the flow in the left to fall to 3.70 grams. There was no increase during the whole time for which the right hand continued in the cold water (seven minutes). The vasoconstriction was therefore intense and durable. When the right hand was immersed in warm water the flow in the left was further diminished to 3.37 grams. The intensity and persistence of the reflex vasoconstriction in this case may pretty safely be taken to indi-

⁶ Simons, A. Arch f Anat u Physiol, 1910, 559

cate that the lesion in the motor neurons has not extended to the vasomotor cells in the cord or to the efferent paths from them. Since the pathologic change appears to be a system disease affecting the motor neurons but sparing the sensory neurons, there is nothing strange in its avoiding the vasomotor neurons also.

TABLE 10—CALORIMETRIC MEASUREMENTS IN CASE OF MRS. MARY N

Time	Right	Left	Room	Time	Right	Left	Room
2 37½	29 62	29 61	23 6	2 57		30 13	23 9
2 39	29 60	29 58		2 58		30 14	
2 40	29 64	29 61		2 59		30 16	
2 41	29 69	29 64		3 00		30 17	
2 42	29 72	29 69		3 01		30 18	
2 43	29 78	29 73	24 0	3 02		30 20	
2 44	29 82	29 78		3 03		30 22	
2 45	29 86	29 82		3 04		30 22	
2 46	29 89	29 86		3 05		30 24	
2 47	29 92	29 90		3 06		30 24	
2 48	29 97	29 93	23 3	3 07		30 25	
2 49	30 00	29 96		3 08		30 28	
2 50	30 04	30 00		3 09		30 30	
2 51	30 07	30 03	23 3	3 10		30 33	
2 52	30 10	30 06		3 11		30 36	
2 53		30 07		3 12		30 37	
2 54		30 09		3 14		30 39	
2 55		30 11		3 15	29 85		
2 56		30 12		3 36	29 64	30 16	

Cooling of calorimeters, R, 0.25 C in twenty-three minutes, L, 0.23 C in twenty-two minutes. Volume of right hand 340 c.c., of left hand 320 c.c.

Another case (Stanislas C.) in which a more or less general atrophy of the extremities, especially the anterior, existed presents certain interesting features. On account of the low degree of intelligence of the patient and his defect of speech the history of the case could not be clearly ascertained. Nor could the defects of sensation which seemed to exist be properly studied. Although this increased the difficulty of making a diagnosis and the true nature of the case was not cleared up, it will not be unprofitable, it is hoped, to quote the blood-flow findings, since they seemed capable of suggesting something toward the diagnosis and of supplementing precisely in such circumstances the examination of the sensory condition.

Stanislas C., a Polish laborer, aged 32, height 5 feet, 6 inches, was admitted to Lakeside Hospital, April 5. The patient complains that he cannot talk properly. Seven months before he was hit by a brick and has since been unable to swallow or talk. He did not lose consciousness. The right supraclavicular region shows a scar from the middle of the clavicle to the top of the scapula. The pupils react promptly to light and accommodation. The mouth tends to be drawn to the right. The tongue protrudes to the right and shows a fine tremor. The soft palate hangs to the right, and the left arch is higher than the right. Blood pressure, 124 systolic, 76 diastolic. General atrophy of muscles of extremities is shown. There is some contracture of the fingers of the right hand. No edema exists. Atrophy is noted of the muscles of the neck, the trapezius, splenius, levator scapulae and serratus. His gait is shuffling but not ataxic. There is no hypotonus of the thigh. All the deep reflexes are exaggerated, except those of the right arm, in which the biceps, triceps and supinator reflexes are gone. There is ankle clonus, but no Babinski or Kernig's sign. Romberg's sign is

very slight. The abdominal and cremasteric reflexes are increased. The right arm is smaller than the left, but the volume measurement showed the left *hand* somewhat atrophied in comparison with the right. Paresis is apparent of the left facial muscles. When asked to smile, the mouth is drawn to the right, but when made to laugh spontaneously both sides are equally used. The right side of the forehead wrinkles more than the left. The vocal cords move very poorly. Then sense of taste is disturbed. His intelligence is very low and does not permit satisfactory examination of sensation. He says that all sensations (temperature, pain, touch, vibration) are better felt over the right side (arm, leg and trunk) than over the left. It is doubtful whether this is true.

The blood flow in the hands was examined April 19. Hands were in bath at 2 25 p. m., in calorimeters at 2 39. Mouth temperature 36.8 C. Pulse 72. At 2 50½ p. m. the left hand was immersed in water at 12 C. At 2 55½ p. m. the left hand was dried and wrapped up. At 2 59¼ p. m. the left hand was put into water at 43.5 C. At 3 06 the left hand was put into water at 9 C. At 3 13 left hand was dried and wrapped up. At 3 17 right hand was removed from calorimeter.

TABLE 11—CALORIMETRIC MEASUREMENTS IN CASE OF STANISLAS C

Time	Right	Left	Room	Time	Right	Left	Room
2 38	29 90	29 93	23 7	3 00	30 80		23 5
2 40	29 91	29 89		3 01	30 87		
2 41	29 94	29 90		3 02	30 91		
2 42	29 97	29 89		3 03	30 99		23 6
2 43	29 99	29 90		3 04	31 07		
2 44	30 02	29 90	23 8	3 05	31 12		
2 45	30 07	29 90		3 06	31 18		
2 46	30 10	29 91		3 07	31 22		23 7
2 47	30 17	29 91	23 6	3 08	31 27		
2 48	30 21	29 91	23 6	3 09	31 32		
2 49	30 25	29 92		3 10	31 39		
2 50	30 30	29 92	23 8	3 11	31 45		
2 51	30 35			3 12	31 49		
2 52	30 39		23 7	3 13	31 56		23 6
2 53	30 43			3 14	31 60		
2 54	30 49			3 15	31 65		23 5
2 55	30 57		23 6	3 16	31 70		
2 56	30 60			3 17	31 77		23 5
2 57	30 65			3 17½		29 68	
2 58	30 71			3 28	31 63	29 60	
2 59	30 78						

Cooling of calorimeters, R, 0.14 C. in eleven minutes, L, 0.32 C. in thirty-eight minutes. Volume of right hand in calorimeter 486 c.c., of left hand 422 c.c.

The flow in the right hand came out 7.0 grams and in the left only 1.47 grams per 100 c.c. per minute (for six minutes before the vaso-motor test) the greatest difference between the two hands which has been observed in the whole series of observations. Measurement showed that the left hand was atrophied in comparison with the right. On immersing the left hand in cold water (for four minutes) the flow in the right increased to 7.85 grams per 100 c.c. per minute. When the left hand was dried and wrapped up, the flow in the right hand rose to 9.55 grams, to increase further to 10.28 grams on immersion of the left hand in warm water. A subsequent immersion of the left hand in cold water produced no effect on the flow unless to keep it stationary, and when the left hand was again wrapped up the flow in the right increased to 10.88 grams. These anomalous results in the reflex vaso-

motor tests have scarcely any parallel in our series of observations. The most obvious explanation would be that the left hand was insensitive to cold, and the entire passivity of the patient when the hand was immersed in water at 9 C, which usually produces some discomfort, lends support to the suggestion. The initial vasoconstriction produced by immersion of the contralateral hand in warm water was also absent in this case, and again the suggestion is plausible that the left hand was insensible to warmth. The steady increase in the flow of the right hand during the whole course of the vasomotor tests would then be due simply to a spontaneously increasing vasodilatation unaffected by impulses from the left hand. While it would be rash to lay stress on isolated observations of this kind, it may be further pointed out that the marked deficiency of the blood flow in the left hand as compared with the right would agree well with a suggestion made when the diagnosis was being considered, that the general condition was superposed on an old left-side hemiplegia. For as we shall see directly, in the hemiplegias examined there was always a deficiency in blood flow in the paralyzed hand. The paresis of the left side of the face would also fit in with this. On the other hand the apparent absence of reflex vasomotor response in the right hand when the left was immersed in warm or cold water would agree with another suggestion made, that a syringomyelia (of the bulb) existed. In any case it seems reasonably clear that in circumstances in which the subjective response of the patient to warmth and cold cannot be studied information might be obtained by an objective method, namely, the study of the vasomotor reflex response.

HEMIPLEGIA

In the four cases of hemiplegia examined the flow in the paralyzed hand was always inferior to that in the normal hand. In C, a man aged 57, with hemiplegia of nine years' standing (paralysis of the left side of the face, left arm and leg) from which there had been very little recovery, the flow in the right hand was 9.15 grams and in the left only 4.67 grams per 100 c.c. per minute, with room temperature 22.2 C. During immersion of the right hand in warm water the flow in the left was 4.31 grams per 100 c.c. per minute for a period of nine minutes, and exactly the same during immersion of the right hand in cold water for a period of seven minutes. In this case there was no question of any defect of conduction in the afferent segment of the reflex vasomotor arc, since it was the normal hand which was subjected to the warmth and cold stimulation, and these sensations were perfectly perceived. The absence of the vasomotor reflex in this old-standing paralysis was interpreted as probably due to anatomic changes in the vessels of the atrophied left hand, including changes in the efferent

vasomotor nerves of the hand and their terminations The protocol of the case has already been published⁷ In the other cases of hemiplegia in which the vasomotor reflexes were examined, evidence was obtained of the activity of the vasomotors of the paralyzed hand, reflex vasoconstriction, however, predominating over reflex vasodilatation

Mrs Eva M, aged 56, was admitted to the City Hospital, Sept 11, 1911, with hemiplegia (left side) On September 5 she lost control of left hand, arm, and leg, fell to the floor but was at no time unconscious and retained the power of speech When admitted the patient's face seemed unaffected, the tongue protruded in the median line There was no paralysis of the palate Complete loss of power and marked loss of tone in arm and leg were noted The biceps and triceps reflexes of the left arm were absent The knee-jerk was absent Babinski's sign was present on the left side Sense of position was lost in the left arm and leg The sense of heat and cold was intact in the left arm and left leg above a level 4 cm below the knee Pain sense was lost in the left arm below the shoulder and in the left leg below the knee Some loss of pain sensibility was found between the left knee and the hip

The blood flow in the hands was examined April 16, 1912 At this time there had been noticeable improvement in the left leg, but not in the arm or hand The hands were in bath at 3 21 p m, in calorimeters at 3 32, out of calorimeters at 3 52 Mouth temperature 37.45 C Pulse 104 The left hand as it hung down in the water pained her somewhat and therefore the vasomotor reaction was not tested

TABLE 12—CALORIMETRIC MEASUREMENTS IN CASE OF MRS EVA M

Time	Right	Left	Room	Time	Right	Left	Room
3 33	30 53	30 41	23.7	3 41	30 76	30 53	23.3
3 34	30 50	30 43		3 45	30 79	30 60	
3 35	30 55	30 46		3 46	30 81	30 61	
3 36	30 59	30 48		3 47	30 84.5	30 63	
3 37	30 62	30 50		3 48	30 88	30 64.5	
3 38	30 63.5	30 52	22.7	3 49	30 90	30 66	
3 39	30 65	30 52.5		3 50	30 93	30 68	
3 40	30 67	30 53		3 51	30 95	30 70	
3 41	30 69	30 53.5		3 52	30 99	30 73	
3 42	30 70	30 54		4 02	30 88	30 63	
3 43	30 72	30 55.5					

Cooling of calorimeters in ten minutes, R, 0.11 C, L, 0.10 C Volume of right hand 334 c c, of left hand 328 c c Water equivalent of calorimeters with contents, R, 3.362, L, 3.357

The flow in the right hand in Mrs Eva M was 6.30 grams and in the paralyzed left hand 4.38 grams per 100 c c per minute with average room temperature 23 C

George H, a man aged about 40 years, with typical motor aphasia and paralysis of the right arm and leg of 4 years' standing, had a blood flow of 7.26 grams per 100 c c per minute in the right hand and 9.82 grams in the left hand with room temperature 26.5 C The ratio between the flows in the two hands was 1.135 During immersion of the left hand in cold water the flow in the right hand sank to 5.04 grams for the first three minutes and then increased to 7.93 grams per

⁷ Heart, 1911, III, 81

100 c c per minute for the next seven minutes. Immersion of the left hand in warm water coincided with a further and persistent diminution of the flow in the right to 5.74 grams. It is possible that the vasoconstriction was merely that not infrequently seen at the close of an experiment and does not represent an abnormally great prolongation of the initial vasoconstriction produced by the application of warmth to the contralateral hand. But the duration of the experiment was by no means great and it is at the end of long experiments that spontaneous and long-lasting diminution in the flow is apt to be witnessed. It seems more probable that there is an abnormal tendency to vasoconstriction in the paralyzed hand.

A week later, the flow was again measured in George H. and came out 9.38 grams for the right hand, and 13.21 grams for the left with room temperature 25.5 C. The ratio between the flows was 1.140, practically the same as at the previous examination. This indicates that the increase in the flow was due mainly at least to increased action of the heart and it is rather curious that the ratio of the pulse frequencies (1.126) agrees almost exactly with the ratio of the blood flows in the paralyzed hand at the two examinations (1.129). If the hand flows in this patient can be taken as an index of the heart output, which is justifiable at any rate so far as the absence of anemia is concerned,⁸ this result would support the conclusion of Yandell Henderson⁹ that with slow heart rates the minute output is proportional to the pulse frequency. There is no reason for thinking that the increased hand flows are due to a vasodilatation affecting the two hands in exactly the same proportion. In any case the external temperature could not be responsible for such an increase as it was about a degree lower at the second examination.

The flow in the feet of George H. was also examined on July 25, and came out 1.63 grams per 100 c c per minute for the right foot and 1.77 grams for the left. These flows in proportion to the hand flows are considerably below the normal.

George H. was admitted to the City Hospital, Oct. 5, 1909, with motor aphasia and paralysis of right arm and leg. He became paralyzed in 1908. When admitted he was unable to protrude the tongue. The right side of chest was markedly smaller than the left. There was a slight increase in the deep reflexes in the right arm and leg. The spinal fluid, 40 drops to minute, was clear, with 2 to 4 white cells to the c c and no Noguchi reaction. The blood flow in the hands was examined on July 18, and in the hands and feet on July 25, 1912. At this time aphasia is still complete. He seems to understand everything, but can only express assent or dissent by gestures. He can lift his arm to some extent but cannot move his left hand. He walks with a crutch and can stand by holding the back of a chair slightly. He can protrude the tongue easily in the median line and he can write. The knee-jerk is stronger on the

⁸ Jour. Exper. Med., 1913, xviii, 113.

⁹ Am. Jour. Physiol., 1913, lxxi, 288.

right side than on the left Ankle clonus is present on the right but not on the left side There is no defect of sensation Some external squint of right eye and diplopia is present No ptosis exists

Blood flow examination of George H, July 18, 1912 Hands were in bath at 2 04 p m, in calorimeters at 2 15 Some minutes elapsed before the right hand was got properly into the calorimeter At 2 31 p m left hand was put into water at 8 C Pulse 68 At 2 41 left hand was put into water at 43 C At 2 51 right hand was removed from calorimeter

TABLE 13—CALORIMETRIC MEASUREMENTS IN CASE OF GEORGE H

Time	Right	Left	Room	Time	Right	Left	Room
2 14	31 52	31 45	26 5	2 36	32 135		
2 19	31 54	31 64		2 37	32 18		
2 20	31 58	31 68	26 6	2 38	32 22		26 4
2 21	31 61	31 75		2 39	32 25		
2 22	31 64	31 79		2 40	32 28		
2 23	31 69	31 87	26 8	2 41	32 295		
2 24	31 72	31 93		2 42	32 31		
2 25	31 76	31 98		2 43	32 33		26 4
2 26	31 79	32 045		2 44	32 365		
2 27	31 825	32 08	26 7	2 45	32 38		
2 28	31 87	32 14		2 46	32 395		26 4
2 29	31 90	32 175		2 47	32 42		
2 30	31 935	32 24		2 48	32 45		
2 31	31 98	32 28		2 49	32 475		
2 32	32 005			2 50	32 50		
2 33	32 025		26 7	2 51	32 52		
2 34	32 04			3 18	32 25	31 87	
2 35	32 10						

Cooling of calorimeters, R, 0 27 C in twenty-seven minutes, L, 0 41 C in forty-seven minutes Volume of right hand 464 cc, of left hand 500 cc Mouth temperature 36 95 C Blood pressure left arm, systolic 90, 82 (sound gone) Another observation 92, 85

Blood flow examination of George H, July 25, 1912 Results on the flow in the feet are given in the general table

The hands were in bath at 2 46½ p m, in calorimeters at 2 56, out of calorimeters at 3 09

TABLE 14—CALORIMETRIC MEASUREMENTS IN CASE OF GEORGE H

Time	Right	Left	Room	Time	Right	Left	Room
2 54	31 38	31 36	25 2	3 04	31 75	31 945	25 55
2 57	31 38	31 39		3 05	31 80	32 00	
2 58	31 43	31 47	25 4	3 06	31 85	32 075	25 7
2 59	31 49	31 58		3 07	31 89	32 165	
3 00	31 53	31 65	25 7	3 08	31 91	32 23	25 7
3 01	31 59	31 73		3 09	31 92	32 27	
3 02	31 66	31 795	25 5	3 17	31 82	32 17	
3 03	31 72	31 865					

Cooling of calorimeters in eight minutes, 0 10 C for R and L Volume of right hand 455 cc, of left 497 cc Water equivalent of hand calorimeters and contents, R, 3,459, L, 3,492 Rectal temperature 37 4 C

Dennis H, a structural iron worker, aged 41, was admitted to the City Hospital, June 19, 1911, with hemiplegia of the left side Walking along the street on July 15, he fell unconscious and remained so about fifteen minutes He had been a hard drinker, had gonorrhea and probably lues No anemia was present (hemoglobin 100 per cent) The tongue protruded in the median line The head was held toward the right rather than the left He was unable to move the left arm and leg The patellar, Achilles, biceps and triceps reflexes on the left side were exaggerated No Babinski sign or ankle clonus was

present. Epicritic and protopathic sensations over left leg were gone. Deep sensibility was present. Epicritic, protopathic, and deep sensibility was present in the arm but was greatly diminished. The same was true over the left side of the neck and face. No loss of power was seen in the face. Systolic blood pressure varied from 140 to 118 during the period of observation. On April 11, 1912, the blood flow in the hands was measured. At this time the left leg had recovered considerably, although he still used it very little. The left hand and arm were still quite powerless.

For the first six minutes in the calorimeters the flow in the right hand was 2.84 grams and in the left 1.80 grams per 100 c c per minute. During the immersion of the hands in the calorimeters the flow continued to increase gradually in both hands but particularly in the left so that for the whole period of immersion in the calorimeters (seventeen minutes) the flows came out 4.19 grams and 3.75 grams per 100 c c per minute for the right and left hands respectively. For the last six minutes of this period the flows were 4.92 grams for the right and 4.80 grams for the left hand. This gradual increase of the flow is observed under two conditions, first, when the flow is permanently small, and secondly, when an initial vasoconstriction is present, due either to nervousness on the part of the patient or to an abnormal sensitiveness of the vasomotor mechanism to the procedures necessarily involved in the measurement. In the case of Dennis H. both of these circumstances probably conspired. That a considerable tendency to vasoconstriction exists in the paralyzed hand was shown in the tests of the vasomotor reflexes. When the right hand was immersed in cold water the flow in the left was reduced from 4.80 grams to 3.49 grams per 100 c c per minute for the first seven minutes, to rise to 5.90 grams per 100 c c per minute for the remaining seven minutes of immersion of the right hand in the cold water. This constitutes a fair reflex vasoconstriction, particularly considering the small initial flow, and it endures, if anything, longer than normal. The moderate vasodilatation which succeeded was rather diminished than increased by subsequent immersion of the right hand in warm water.

TABES DORSALIS

In the five cases of tabes examined, the flow in both hands and feet was found subnormal, the deficiency being greater in the feet than in the hands. The vasomotor reflexes were quite feeble. The poor reflex response is especially striking when coupled with distinct or even acute perception of the sensations of cold and warmth, as in the case of Joseph S.

Joseph S., a laborer, aged 54, was admitted to the City Hospital, August 5, with tabes dorsalis. He had had pain and "funny feelings" for five years in both legs. Says he cannot feel over the hands or feet, but feels pin pricks somewhat. He also complains of sphincter trouble, and has a history of gonorrhea and lues. The spinal fluid, 120 drops per minute, 200 cells per c c, shows

a strongly positive Noguchi reaction The pupils, pin point, react to accommodation There is little if any reaction to light The nasal septum is perforated Heart examination is negative There is marked arteriosclerosis Knee-jerk, Achilles and cremasteric reflexes are absent Romberg sign is marked Muscular incoordination is shown

The blood flow in the hands and feet was measured August 7 Pulse 124 Hands in bath at 1 46½ p m, in calorimeters at 1 57¼ p m At 2 12 left hand immersed in water at 8.4 C He feels that the water is cold and soon begins to complain of it, withdrawing the hand momentarily At 2 24 left hand put into water at 42.8 C At 2 35 right hand removed from calorimeter

TABLE 15—CALORIMETRIC MEASUREMENTS IN CASE OF JOSEPH S

Time	Right	Left	Room	Time	Right	Left	Room
1 57	31.20	31.13		2 18	31.785		25.0
1 59	31.22	31.15	24.9	2 19	31.81		
2 00	31.26	31.18		2 20	31.83		
2 01	31.295	31.20	25.1	2 21	31.865		
2 02	31.325	31.22		2 22	31.895		
2 03	31.365	31.255		2 23	31.91		
2 04	31.40	31.27	25.0	2 24	31.935		
2 05	31.43	31.295		2 25	31.96		25.0
2 06	31.46	31.315		2 26	31.985		
2 07	31.495	31.35	25.1	2 27	32.00		
2 08	31.52	31.365		2 28	32.025		25.15
2 09	31.56	31.38		2 29	32.05		
2 10	31.58	31.405	25.1	2 30	32.08		
2 11	31.605	31.43		2 31	32.09		
2 12	31.63	31.45		2 32	32.11		
2 13	31.67		25.0	2 33	32.13		25.4
2 14	31.695			2 34	32.16		
2 15	31.705			2 35	32.19		
2 16	31.73			2 15	32.075	31.13	
2 17	31.76						

Cooling of calorimeters, R, 0.115 C in ten minutes, L, 0.32 C in thirty-three minutes Volume of right hand in calorimeter 425 cc, of left hand 441 cc He is right handed, but from the way in which he held his hand, a somewhat smaller proportion of the right hand was in the calorimeter than of the left This is taken account of in the volume measurement

The flow in the right foot in this patient was 0.76 gram and in the left foot 0.88 gram per 100 cc per minute with the relatively high room temperature 25 C The flow in the right hand was 5.86 grams and in the left 4.33 grams with the same room temperature Probably the inequality in the flows in the two hands is not so great as it appears to be For, as has been mentioned in the protocol, the right hand was not inserted so deeply into the calorimeter as the left, and it has been shown that the flow per unit of volume is greater in the distal than in the proximal portions of the hand, corresponding with the relatively greater surface However, in our study of diseases of the nervous system there have been numerous instances of the existence of inequalities of flow in the two hands or feet which could not be connected with any known cause It may indeed be said that such inequalities are common features of those diseases It has been suggested that vasomotor conditions, probably essentially connected with the pathology

or pathologic physiology of the morbid state, are responsible for these inequalities ¹⁰

On immersion of the left hand (of Joseph S) in cold water, which apparently caused him considerable discomfort, the flow in the right was but slightly changed, falling to 5.21 grams per 100 c c per minute for the first four minutes and then rising slightly again to 5.43 grams per 100 c c per minute for the remaining eight minutes of the immersion. This is truly an insignificant vasoconstrictor reaction. Immersion of the left hand in warm water caused a slight diminution of the flow in the right, to 5.22 grams per 100 c c per minute for the first five minutes, which then gave place to a correspondingly slight increase (to 5.48 grams for the next six minutes). Such slight reflex vasomotor effects have certainly rarely been observed in other conditions. It must be noted, however, that decided arteriosclerosis was present in this man and this condition is itself associated with relatively small vasomotor reflexes ¹¹

In a case of tabes examined at the dispensary (Abe K) the hand flows were only 1.27 grams for the right and 1.22 grams for the left, with room temperature 23 C. Probably the circulatory condition noted in the protocol was a factor in the small flow, as there was evidence of some loss of cardiac compensation (cyanosis, edema of legs and feet)

Abe K, a waiter, aged 59, was admitted to the dispensary January 30. Six weeks ago he began to lose his sight and is now almost blind. For two months he has been unsteady on his feet, especially in walking at night. Some exophthalmos is noted. Slight ptosis of both eyes exists. The face and lips are cyanotic. The pupils are irregular, fixed, unequal with no reaction to light or accommodation. His gait is uncertain, with left foot flapped. The knee-jerk is much diminished. The Achilles reflex is absent. There is no Babinski sign. Edema of feet and legs is present, with hypotonus of muscles. Sensibility to touch, pain, heat and cold is diminished below the knees. The muscle sense is not good. There is incoordination of the hands. There is a slight Romberg sign. Examination of lungs is negative. The heart dulness extends 2 cm to the left of the nipple line. There is also increase of dulness to the right of the sternum. The aortic second sound is much accentuated. The edge of the liver is palpable 3 finger breadths below the costal margin on deep inspiration. The blood flow in the hands was measured on February 1.

W. B. C., a cigarmaker, aged 57, was admitted to Lakeside Hospital, November 8, with tabes dorsalis. He complains of difficulty in walking and ataxia, most marked in left leg. There are no sensory disturbances, except that he does not feel hot water on his feet unless it is pretty hot. Up to the present illness his eyesight has been good. There is external strabismus of the right eye. The pupils are unequal and irregular and do not react to light, but react to accommodation. Knee-jerk is absent. The hands are ataxic, he has difficulty in buttoning his clothes. Examination of heart and lungs is negative. The blood flow was examined November 11.

¹⁰ Paper XII of this series

¹¹ Stewart, G. N. The Blood Flow in the Hands and Feet in Certain Diseased Conditions of the Vessels or of Their Nervous Mechanism, *THE ARCHIVES INT. MED.*, 1914, xiii, 177

The feet were in bath at 2 23 p m, in calorimeters at 2 36 At 3 07 the left foot was put into water at 44 3 C He feels it comfortably warm At 3 19 right foot was taken out of calorimeter Pulse 84

TABLE 16—CALORIMETRIC MEASUREMENTS IN CASE OF W B C

Time	Right	Left	Room	Time	Right	Left	Room
2 34	31 33	31 26	20 9	3 01	30 97	31 03	22 0
2 37	31 23	31 18	20 9	3 03	30 95	31 01	22 0
2 39	31 22	31 17	20 9	3 05	30 925	30 99	21 9
2 41	31 19	31 155		3 07	30 90	30 98	
2 43	31 17	31 135	20 9	3 09	30 89		21 9
2 45	31 14	31 13	21 2	3 11	30 88		21 8
2 47	31 11	31 10	21 3	3 13	30 865		21 7
2 49	31 09	31 085	21 3	3 15	30 84		21 7
2 51	31 065	31 07	21 35	3 17	30 825		
2 53	31 04	31 06	21 4	3 19	30 81		21 9
2 55	31 03	31 055	21 7	3 21	30 74	30 68	
2 57	31 01	31 05	21 8	3 34	30 52	30 47	
2 59	30 99	31 04	21 8				

Cooling of foot calorimeters in thirteen minutes, R, 022 C, L, 021 C Volume of right foot 925 cc, of left foot 943 cc Water equivalent of feet calorimeters with contents, R, 3,660, L, 3,673

The hands were in bath at 3 40 p m, in calorimeters at 3 48 $\frac{3}{4}$ At 4 06 the left hand was put into water at 44 7 C He feels it warm At 4 20 left hand was put into water at 13 C He feels it rather cold Right hand taken out of calorimeter at 4 29 p m

TABLE 17—CALORIMETRIC MEASUREMENTS IN CASE OF W B C

Time	Right	Left	Room	Time	Right	Left	Room
3 48	31 75	31 76		4 10	31 89		22 9
3 50	31 74	31 75	23 3	4 11	31 89		
3 51	31 73	31 74	23 2	4 12	31 90		22 7
3 52	31 73	31 74		4 13	31 90		
3 53	31 74	31 75	23 2	4 14	31 91		22 8
3 54	31 74	31 75	23 2	4 15	31 93		
3 55	31 75	31 75		4 16	31 95		22 9
3 56	31 76	31 755	23 1	4 17	31 97		
3 57	31 77	31 765		4 18	31 99		22 9
3 58	31 78	31 775		4 19	31 99		
3 59	31 79	31 785	23 0	4 20	32 01		
4 00	31 80	31 80		4 21	32 01		22 8
4 01	31 81	31 82	22 9	4 22	32 02		
4 02	31 82	31 83		4 23	32 03		22 5
4 03	31 835	31 84	22 9	4 24	32 04		
4 04	31 85	31 85		4 25	32 05		22 7
4 05	31 86	31 86	23 0	4 26	32 06		
4 06	31 87	31 86		4 27	32 065		22 5
4 07	31 88			4 28	32 07		
4 08	31 89		23 0	4 29	32 08		22 7
4 09	31 89			4 38	31 95	31 44	

Cooling of hand calorimeters, R, 013 C in nine minutes, L, 042 C in thirty-two minutes Volume of right hand 380 cc, of left 388 cc Water equivalent of hand calorimeters with contents, R, 3,399, L, 3,405 Rectal temperature 36 90 C

In W B C the blood flow in the right foot was 0 54 gram and in the left foot 0 87 gram per 100 cc per minute with room temperature 21 5 C During immersion of the left foot (for a period of twelve minutes) in warm water, the flow in the right was 0 75 gram per 100 cc per minute The hand flows before testing the vasomotor reaction

were 5.42 grams for the right, and 5.05 grams for the left with room temperature 22.9 C. Immersion of the left hand in warm water reduced the flow in the right (for the first five minutes) to 4.01 grams per 100 c c per minute. For the remaining nine minutes of the period of immersion, the flow in the right hand rose to 6.16 grams per 100 c c per minute. A subsequent immersion of the left hand in cold water caused a diminution in the flow in the right to 3.26 grams but only for a single minute, the flow then rising for the remainder of the period of immersion to 5.3 grams per 100 c c per minute.

Gabriel M., a barber, aged 41, was admitted to Lakeside Hospital, November 13, with the diagnosis of tabes. He complains of seeing double, that the left leg is weaker than the right and that he gets tired in walking. The patellar and Achilles reflexes are absent from both sides. The biceps and triceps reflexes are present in both arms. The plantar reflex is normal. There is marked hypotonus of the iliofemoral muscles with ataxia. There is ataxia also of the toes. Vibration is everywhere perceived. Hypesthesia to the needle is noted in both lower extremities, with great delay in transmission. Over the left leg the delay is fully two seconds. Romberg's sign is positive. The spinal fluid is clear under normal pressure, the cell count 8, Noguchi negative, Wassermann strongly positive. The grip of the hands is fairly strong. There is no incoordination of the hand movements. Sometimes a good deal of pain is present in the legs especially at night. The feet are habitually cold. Particulars of the first examination of the blood flow in the hands on November 17 are given in the general table.

Second examination of blood flow in Gabriel M., November 19. Hands in bath at 3.43 p m., in the calorimeters at 3.52. At 4.10 p m. the left hand was put into water at 43 C. At 4.20 p m. the right hand was taken out of the calorimeter. Pulse 100.

TABLE 18—CALORIMETRIC MEASUREMENTS IN SECOND EXAMINATION OF GABRIEL M.

Time	Right	Left	Room	Time	Right	Left	Room
3 51	31.73	31.64		4 07	31.75	31.65	24.15
3 53	31.72	31.63	24.0	4 08	31.755	31.655	
3 54	31.715	31.625	24.0	4 09	31.76	31.66	24.2
3 55	31.71	31.62		4 10	31.765	31.66	
3 56	31.71	31.62	24.0	4 11	31.77		
3 57	31.705	31.61		4 12	31.77		24.2
3 58	31.71	31.62	24.1	4 13	31.78		
3 59	31.715	31.63		4 14	31.78		24.2
4 00	31.72	31.635	24.1	4 15	31.79		
4 01	31.72	31.63		4 16	31.795		24.3
4 02	31.72	31.63	24.1	4 17	31.795		
4 03	31.725	31.635		4 18	31.795		24.4
4 04	31.73	31.64		4 19	31.80		24.3
4 05	31.735	31.645	24.2	4 20	31.81		
4 06	31.74	31.65		4 33	31.65		

Cooling of hand calorimeters, R, 0.16 C in thirteen minutes, L, 0.29 C in twenty-three minutes. Volume of right hand, 424 c c, of left 407 c c. Water equivalent of calorimeters with contents, R, 3,434, L, 3,420. Rectal temperature 37.20 C.

Third examination of blood flow in Gabriel M., November 24. Feet in bath at 2.45 p m., in calorimeters at 2.56. At 3.44 right foot put into water at 43 C. At 3.58 right foot put into water at 8.7 C. He felt it very cold at first. At 4.12 p m. left foot taken out of calorimeter.

TABLE 19—CALORIMETRIC MEASUREMENTS IN THIRD EXAMINATION OF GABRIEL M

Time	Right	Left	Room	Time	Right	Left	Room
2 55	31 82	31 86	20 1	3 38	30 88	30 94	22 3
2 58	31 63	31 66		3 40	30 87	30 93	
3 00	31 54	31 57		3 42	30 87	30 92	
3 02	31 47	31 52	20 3	3 44	30 86	30 90	
3 04	31 39	31 45	20 7	3 46	30 795	30 885	22 4
3 06	31 32	31 39	20 8	3 48		30 87	22 5
3 08	31 26	31 35	21 0	3 50		30 865	22 6
3 10	31 21	31 29	21 0	3 52		30 86	22 6
3 12	31 17	31 25	21 1	3 54		30 855	22 6
3 14	31 12	31 20	21 2	3 56		30 85	22 7
3 16	31 08	31 16	21 3	3 58		30 845	
3 18	31 05	31 13	21 4	4 00		30 835	22 8
3 20	31 01	31 10	21 5	4 02		30 83	22 8
3 22	30 98	31 07	21 7	4 04		30 82	
3 24	30 96	31 05	21 7	4 06		30 81	22 9
3 26	30 94	31 03	21 9	4 08		30 80	23 1
3 28	30 92	31 01	22 0	4 10		30 79	22 9
3 30	30 90	30 985		4 12		30 77	
3 32	30 895	30 97	22 1	4 13		30 755	
3 34	30 89	30 955	22 2	4 27	30 09	30 52	
3 36	30 88	30 95	22 2				

Cooling of foot calorimeters, R, 0 705 C in forty-one minutes, L, 0 235 C in fourteen minutes Volume of right foot 1,092 cc, of left 1,087 cc Water equivalent of foot calorimeters with contents R, 3,783, L, 3,779 Pulse 108

Hands in bath at 4 33½ p m, in calorimeters at 4 32, out of calorimeters at 4 43

TABLE 20—CALORIMETRIC MEASUREMENTS IN THIRD EXAMINATION OF GABRIEL M

Time	Right	Left	Room	Time	Right	Left	Room
4 31	31 48	31 39	24 2	4 39	31 41	31 855	
4 33	31 42	31 36	24 7	4 40	31 41	31 255	23 4
4 34	31 42	31 36	24 5	4 41	31 41	31 365	
4 35	31 415	31 355	24 2	4 42	31 41	31 865	
4 36	31 42	31 36		4 43	31 42	31 87	23 9
4 37	31 42	31 36	23 7	4 49	31 32	31 28	
4 38	31 41	31 36	23 4				

Cooling of hand calorimeters in six minutes, R, 0 10 C, L, 0 09 C Rectal temperature 37 55 C Volume of right hand 425 cc, of left 390 cc Water equivalent of hand calorimeters with contents, R, 3,435, L, 3,407

The flow in the right hand of Gabriel M at the first examination was 1 0 gram, in the left 1 37 grams per 100 cc per minute with room temperature 22 6 C Two days later the flows were 2 91 grams and 2 86 grams for the right and left hands respectively with the higher room temperature of 23 9 C Immersion of the left hand in warm water caused scarcely any increase of flow in the right hand, which came out 3 07 grams per 100 cc per minute during the ten minutes of the period of immersion The flow in the right foot at the same examination was 0 56 gram, and in the left 0 62 gram The ratio of the combined foot flows to the combined hand flows was 1 4 89, indicating a relatively greater deficiency in the feet than in the hands. This is characteristic of all the cases of tabes examined For a period

of twenty-two minutes immersion of the right foot in warm water the flow in the left foot was slightly increased (to 0.89 gram per 100 c c per minute)

At the third examination the flow in the right hand of Gabriel M was 2.77 grams and in the left hand 2.88 grams with room temperature 22.1 C. The flow in the right foot before testing of the vasomotor reflexes was 0.96 gram and in the left foot 0.73 gram. The ratio of the combined foot to the combined hand flows was 1.393. During immersion of the right foot in warm water the flow in the left foot (for the first four minutes of the immersion) sank to 0.65 gram, and then rose to 0.92 gram per 100 c c per minute for the remaining ten minutes of the immersion period. When the right foot was subsequently put into cold water the change was slight, the flow in the left foot being 0.84 gram per 100 c c per minute for the first four minutes of the immersion and 0.70 gram for the remaining ten minutes.

TABLE 21—CALORIMETRIC MEASUREMENTS IN SECOND EXAMINATION OF JOHN M

Time	Right	Left	Room	Time	Right	Left	Room
2 14	31.79	31.68		2 31	32.115		24.4
2 15	31.77	31.67		2 32	32.15		
2 16	31.78	31.68	23.8	2 33	32.185		24.7
2 17	31.785	31.69		2 34	32.21		
2 18	31.795	31.70		2 35	32.24		
2 19	31.82	31.73	24.4	2 36	32.28		
2 20	31.85	31.76	24.2	2 37	32.31		24.8
2 21	31.88	31.79		2 38	32.335		
2 22	31.90	31.82		2 39	32.37		24.5
2 23	31.92	31.85		2 40	32.395		
2 24	31.94	31.87	23.9	2 41	32.42		24.0
2 25	31.98	31.90		2 42	32.45		
2 26	32.00	31.93		2 43	32.49		23.4
2 27	32.025		24.1	2 44	32.52		23.4
2 28	32.05			2 45	32.57		23.8
2 29	32.07		24.2	2 52	32.47	31.55	
2 30	32.09						

Cooling of hand calorimeters, R, 0.10 C in seven minutes, L, 0.38 C in twenty-six minutes. Volume of right hand 426 cc, of left 399 cc. Water equivalent of hand calorimeters with contents, R, 3,436, L, 3,414. Pulse 96.

John M, a laborer, aged 45, was admitted December 2 at Lakeside Hospital with the diagnosis of tabes, complaining of incontinence of urine and trouble in walking. A history was given of gonorrhea. He says he was bit in the arm twenty-eight years ago by a person supposed to have had lues. He denies having had chancre. His present illness seems to have commenced fourteen years ago. The reflexes are hypo-active in the biceps and supinator of both arms. The lower extremities are ataxic. The patellar and ankle reflexes are absent, also the plantar reflexes. There is no Babinski or Kernig's sign. Romberg's sign is positive. He feels a point on the feet but the response is slow. He walks fairly well, better than some time ago, he says. The pupils are equal, central and regular, but do not react to light and very sluggishly to accommodation. The skin of the nose is covered entirely by scar tissue, the septum is deficient posteriorly. Blood examination, erythrocytes 4,976,000, white blood corpuscles 6,200, hemoglobin 80 per cent. The blood flow was examined on

December 3 and December 8 The particulars of the flow in the feet at first examination of John M are given in the general table

Second examination of blood flow in John M, Dec 8, 1914 Hands were in bath at 2 05 p m, in calorimeters at 2 14½ At 2 26 p m the left hand was put into water at 8 C At 2 36 p m the left hand was put into water at 43 1 C At 2 45 p m the right hand was taken out of the calorimeter

The feet were in bath at 2 55 p m, in calorimeters at 3 06 At 3 41 p m right foot was put into water at 8 3 C He feels it pretty cold At 3 55 p m left foot taken out of calorimeter.

TABLE 22—CALORIMETRIC MEASUREMENTS IN SECOND EXAMINATION OF JOHN M (FEET)

Time	Right	Left	Room	Time	Right	Left	Room
3 05	32 23	32 23	24.8	3 33	31 93	32 055	24.8
3 08	32 18	32 25	24.8	3 35	31 93	32 055	24.8
3 09	32.15	32 20	24.9	3 37	31 97	32 05	24.8
3 11	32 12	32 17		3 39	31 97	32 05	
3 13	32 11	32 16	24.5	3 41	31 95	32 055	24.8
3 15	32 10	32 155		3 43	31 93	32 055	24.7
3 17	32 09	32 145	24.8	3 45		32 05	24.8
3 19	32 07	32 13	24.9	3 47		32 055	
3 21	32 05	32 11	24.7	3 49		32 05	24.5
3 23	32 02	32 055		3 51		32 045	24.6
3 25	32 00	32 07	24.5	3 53		32 04	24.8
3 27	32 00	32.055		3 55		32 04	
3 29	31 99	32 05	24.5	3 58		31 97	
3 31	31 955	32 05	24.7	4 04	31 51	31 85	

Cooling of foot calorimeters, R, 0 37 C in twenty-one minutes, L, 0 11 C in six minutes Rectal temperature, 37 65 C Volume of right foot, 1,006 c c, of left, 1,001 c c Water equivalent of foot calorimeters with contents, R, 3,720, L, 3,716

In John M at the first examination the flows in the right and left foot respectively, before the vasomotor reflexes were tested, were 1 27 grams and 1 28 grams per 100 c c per minute, with room temperature 24 2 C For a period of twelve minutes immersion of the right foot in cold water the flow in the left was reduced to 0 95 gram per 100 c c per minute Subsequent immersion of the right foot in warm water for a period of fourteen minutes caused an increase of the flow in the left to 1 52 grams per 100 c c per minute Five days later the flow in the right hand was found to be 6 60 grams and in the left 7 57 grams with room temperature 24 C When the left hand was put into cold water the flow in the right fell to 6 46 grams per 100 c c per minute for the first five minutes and then rose for the remaining five minutes of the period of immersion of the left hand, to 8 47 grams per 100 c c per minute, an insignificant reaction When the left hand was subsequently immersed in warm water the flow in the right hand was only increased to 8 79 grams per 100 c c per minute for the whole nine minutes of the period of immersion At the same examination the flow in the right foot came out, before the vasomotor reflexes were tested, 1 35 grams per 100 c c per minute and that in the left foot 1 57 grams, with room temperature 24 7 C The ratio of the combined foot flow to the combined hand flow was 1 4 85 The room was warm and the

patient perspiring, so that the flows both in hands and feet are really more deficient than the actual numbers would suggest, and the same is true for the foot flows at the first examination. When the right foot was immersed in cold water the flow in the left foot was only slightly changed, falling to 1.39 grams per 100 c c per minute for the whole fourteen minutes of the immersion.

The case of Joseph K. is of interest, inasmuch as the suggested diagnosis of malingering was not, as regards the symptoms described in the legs, supported by the blood flow examination, which, on the contrary, indicated a real pathologic condition.

Joseph K., a laborer, aged 48, was admitted to the hospital June 17. There appears to be delayed sensation in the extremities. He says that he does not feel heat or vibratory sensation in the thighs. Pin pricks are apparently not well recognized. Knee-jerk and Achilles reflex are strong. He complains of pain in the left leg. Says he has cold sweats on legs and feet at night in bed. His legs feel cold to his hand, although he expects them to be warm since they are covered with sweat. He pinches his calf and says he feels nothing there. A zone on the calves is apparently anesthetic to contact. In front on the shins

TABLE 23—CALORIMETRIC MEASUREMENTS IN CASE OF JOSEPH K.

Time	Right	Left	Room	Time	Right	Left	Room
1 53	31.13	31.12		2 12	31.905		
1 55	31.12	31.125	27 2	2 13	31.925		27 4
1 56	31.16	31.16		2 14	31.96		
1 57	31.21	31.22		2 15	31.995		
1 58	31.26	31.27	27 2	2 16	32.025		27 4
1 59	31.31	31.325		2 17	32.05		
2 00	31.36	31.36		2 18	32.08		27 5
2 01	31.42	31.41	27 3	2 19	32.12		
2 02	31.49	31.47		2 20	32.165		
2 03	31.54	31.525		2 21	32.205		
2 04	31.605	31.585	27 3	2 22	32.26		
2 05	31.68	31.64		2 23	32.30		27 55
2 06	31.73	31.60		2 24	32.365		
2 07	31.76			2 25	32.42		
2 08	31.79		27 3	2 26	32.48		27 55
2 09	31.80			2 27	32.545		
2 10	31.825			2 33	32.49	31.505	
2 11	31.87						

Cooling of calorimeters, R, 0.055 C in six minutes, L, 0.195 C in twenty-seven minutes. Volume of right hand 495 c c, of left hand 479 c c. Water equivalent of calorimeters with contents, R, 3,491, L, 3,478. Rectal temperature 37.55 C.

at this level he feels contact, as also on the patellae and on the feet. He feels warm water on the feet. He says his hand "shortens" when he tries to write. His pupils react to light and accommodation. The chest examination reveals nothing special. Temperature normal. Blood examination on June 24 gave erythrocytes 5,120,000, leukocytes 9,400, hemoglobin 85 per cent. Two Wassermann tests were negative for blood, as also the Wassermann and Noguchi reactions for spinal fluid. On June 26 pin pricks were better appreciated over the thighs, the knee-jerks were not strong, but were equal on the two sides. The patient was discharged on July 3 "cured," with a suggestion that he was malingering. Blood flow in the hands and feet was examined on June 26. The day was warm.

Hands in bath at 1.41 p m, in calorimeters at 1.54½ p m. At 2.06 p m left hand immersed in cold water (8.5 C). He says he feels the water very

cold At 2 16 p m left hand put into water at 41.4 C At 2 27 the right hand taken out of calorimeter

The flow in the right hand in Joseph K. was 8.94 grams and in the left 8.75 grams per 100 c c per minute with room temperature 27.3 C. For the man's age and the high room temperature, these flows are fair but by no means large, and the slight preponderance in the right hand is entirely normal. The vasomotor reflexes in the hand both to cold and warmth were also normal in intensity and duration. In the feet, on the contrary, the flows came out extremely small, especially taking into account the high room temperature (0.50 grams for the right and 0.54 gram per 100 c c per minute for the left foot, with room temperature 26.4 C). This is quite in agreement with the patient's statement as to the coldness of his feet. Also there was total absence of any vasomotor reflex in the left foot when the right was immersed for ten minutes in warm water, the flow remaining unchanged (0.53 gram). While the patient might have showed some temporary improvement in his not very obtrusive symptoms during his stay in the hospital, it seems unlikely that such definite blood flow results for the feet should be devoid of significance. They at any rate would suggest the necessity in such a case of renewed careful examination of the patient before the suggestion of malingering could be accepted.

In Fred L., a man aged 22, with a glioma of the occipital lobe, the striking feature of the blood-flow examination was the great intensity of the contralateral vasomotor reflexes both to heat and cold. Two examinations were made within eight days and this was clearly seen at both. It is a plausible suggestion that the increased intracranial pressure, of which there were evident symptoms, may have rendered the vasomotor centers hyperexcitable. It is possible also that the rather small flows for the age of the patient might have been due to a peripheral vasoconstriction produced in this way in the interest of the brain circulation.

Fred L. was first admitted to Lakeside Hospital, June 30, 1908. He complained of dizzy attacks and severe headache. The attacks occurred about once a week and varied in intensity. There was never any nausea or vomiting. Severe headaches had occurred nearly every day since his first trouble. Examination of the eyes showed choked disk and hemianopsia. He could not see objects at his right. Hearing, the same on both sides, was a little less acute than normal. Numerous lumbar punctures were made, and finally a decompression operation was done. Two years later he reported to the dispensary much improved. He again reported July 18, 1911, that occipital headache came on at night and prevented sleep. Only large doses of morphin quieted him at all. He was readmitted to the hospital, Oct 8, 1912. Hemianopsia was present as before. The blood flow in the hands was twice examined (Nov 18 and Nov 26, 1912). On November 27 he left the hospital for Thanksgiving and returned on November 28 with severe headache and vomiting. On November 29 an operation was resolved on, during which he died. The necropsy showed a

glioma with cystic degeneration in the left occipital lobe resting on the tentorium The cyst measured about 5 cm by 3 cm

First blood flow examination of Fred L Hands in bath at 3 07 p m, in calorimeters at 3 20½ At 3 38 left hand immersed in water at 43 C Pulse 88 At 3 50 p m the left hand was put into water at 112 C He feels the water very cold At 4 02 right hand was removed from calorimeter

TABLE 24—CALORIMETRIC MEASUREMENTS IN CASE OF FRED L

Time	Right	Left	Room	Time	Right	Left	Room
3 20	30 44	30 42		3 43	30 88		
3 22	30 37	30 40		3 44	30 92		
3 23	30 38	30 41		3 45	30 96		
3 24	30 38	30 42		3 46	31 01		
3 25	30 385	30 43	22 0	3 47	31 06		
3 26	30 41	30 47		3 48	31 09	30 58	
3 27	30 43	30 50	22 1	3 49	31 12		
3 28	30 48	30 53		3 50	31 18		
3 29	30 52	30 565	22 1	3 51	31 18		
3 30	30 58	30 58		3 52	31 185		
3 31	30 60	30 60	22 0	3 53	31 19		
3 32	30 61	30 62		3 54	31 19		23 0
3 33	30 63	30 64	22 0	3 55	31 19		
3 34	30 66	30 68		3 56	31 195		22 8
3 35	30 69	30 70		3 57	31 225		
3 36	30 71	30 71*		3 58	31 245		22 5
3 37	30 71	30 71		3 59	31 25		22 1
3 38	30 73	30 70		4 00	31 27		
3 39	30 74			4 01	31 28		22 2
3 40	30 765			4 02	31 31		
3 41	30 80			4 12	31 19		
3 42	30 83						

Cooling of calorimeters in ten minutes, R, 012 C, L, 011 C Volume of right hand 385 cc, of left 377 cc His hands are thin Water equivalent of calorimeters with contents, R, 3,403, L, 3,397 Rectal temperature 377 C

*He is paying great attention to the preparations for the warm water test

TABLE 25—CALORIMETRIC MEASUREMENTS IN SECOND EXAMINATION OF FRED L

Time	Right	Left	Room	Time	Right	Left	Room
10 57½	31 17	31 19	21 0	11 24		31 785	20 6
11 00	31 195	31 21		11 25		31 795	
11 01	31 205	31 225		11 26		31 80	20 7
11 02	31 21	31 26	21 5	11 27		31 795	
11 03	31 22	31 28		11 28		31 80	
11 04	31 24	31 295	21 5	11 29		31 805	20 7
11 05	31 295	31 31		11 30		31 81	
11 06	31 295	31 335	21 4	11 31		31 82	
11 07	31 32	31 35		11 32		31 82	
11 08	31 34	31 37	21 35	11 33		31 82	20 7
11 09	31 39	31 395		11 34		31 815	
11 10	31 395	31 405		11 35		31 825	
11 11	31 42	31 42		11 36		31 835	
11 12	31 45	31 435		11 37		31 86	20 7
11 13	31 50	31 46		11 38		31 875	
11 14		31 465	20 9	11 39		31 89	20 7
11 15		31 48		11 40		31 90	
11 16		31 505		11 41		31 915	
11 17		31 555	20 7	11 42		31 935	
11 18		31 605		11 43		31 95	20 7
11 19		31 635	20 7	11 44		31 965	
11 20		31 675		11 45		31 975	
11 21		31 69		11 46		31 99	
11 22		31 73	20 6	12 02	30 82	31 725	
11 23		31 76					

Cooling of calorimeters, R, 068 C in 49 minutes, L, 0265 C in sixteen minutes Volume of right hand 389 cc, of left 380 cc Water equivalent of calorimeters with contents, R, 3,406, L, 3,399 Rectal temperature 3775 C

Second blood flow examination of Fred L. He says he is feeling better than at the previous examination though he was sick (vomiting) all yesterday morning. Hands were in bath at 10 45½ a m, in calorimeters at 10 58½. At 11 13 a m the right hand was put into water at 43 C. At 11 24 a m the right hand was put into water at 10.5 C. At 11 35 right hand was again immersed in water at 43 C. At 11 46 right hand was taken out of calorimeter. Pulse 100.

At the first examination the flow in the right hand in Fred L. was 5.43 grams and in the left 4.80 grams per 100 c c per minute with room temperature 22 C (ratio 1.113). Immersion of the left hand in warm water reduced the flow for the first two minutes in the right hand to 4.18 grams per 100 c c per minute. For the remaining ten minutes of the period of immersion the flow in the right hand rose to 8.28 grams per 100 c c per minute, a marked reflex vasodilatation. When the left hand was now immersed in cold water the flow in the right hand fell to 2.28 grams per 100 c c per minute for the first six minutes of the period of immersion. For the remaining six minutes of the period it rose somewhat but only to 4.84 grams. The reflex vasoconstriction was thus very intense and durable. At the second examination the flow for the right hand, before the vasomotor reaction was tested, was 6.15 grams per 100 c c per minute and for the left 5.49 grams with room temperature 21.4 C (ratio 1.112, almost precisely the same as at the previous examination). The vasomotor reflex tests also showed intense and persistent effects.

In a young man (J. S.), recovering from tetanus after antitoxin treatment, vasomotor reflexes fully as intense were observed. There was no direct evidence that this condition was due to the action of the tetanus toxin or antitoxin on the nervous system, but the extent of the crossed vasomotor reflexes was certainly notable.

TABLE 26—CALORIMETRIC MEASUREMENTS IN CASE OF J. S.

Time	Right	Left	Room
1 37	30 53	30 54	25 5
1 39	30 49	30 51	
1 40	30 48	30 49	
1 41	30 47	30 49	
1 42	30 48	30 50	26 0
1 43	30 495	30 52	
1 44	30 51	30 54	
1 45	30 535	30 56	
1 46	30 58	30 61	25 9
1 47	30 61	30 64	
1 48	30 63	30 67	
1 49	30 65	30 72	
1 50	30 68	30 74	26 2
1 51	30 69		
1 52	30 705		
1 53	30 72		

Time	Right	Left	Room
1 54	30 74		26 0
1 55	30 795		
1 56	30 83		
1 57	30 89		
1 58	30 935		26 0
1 59	30 995		
2 00	31 05		
2 01	31 08		
2 02	31 095		25 8
2 03	31 10		
2 04	31 16		
2 05	31 22		
2 06	31 27		30 55
2 07	31 31		
2 08	31 37		
2 17	31 29		

Cooling of calorimeters, R, 0.08 C in nine minutes, L, 0.19 C in twenty-seven minutes. Volume of right hand 389 c c, of left hand 358 c c.

J. S., a young laborer, was admitted to the City Hospital, March 18, suffering from tetanus. On March 9 his right thumb was injured by a machine. On March 16 pain and stiffness were present in the jaw. Three days later his back

was stiff and painful, attacks of cramp-like rigidity occurred. When admitted there was a spastic condition of legs, arms and hands, and some spasm of the jaw. He was treated with large doses of antitoxin. The blood flow in the hands was examined on April 5. The thumb had nearly healed. The knee-jerks were still exaggerated.

The hands were in bath at 1 28 p m, in calorimeters at 1 38. At 1 50 p m the left hand was immersed in water at 43.5 C. At 2 00 p m the left hand was put into water at 7 C. At 2 08 p m the right hand was taken out of the calorimeter. Pulse 92, rather weak. Mouth temperature 37.3 C.

The initial flow in the hands of J. S. was subnormal for his age and the room temperature (5.32 grams per 100 c c per minute for the right hand and 6.3 grams for the left, with room temperature 25.9 C). On immersion of the left hand in warm water the flow in the right fell to 3.32 grams per 100 c c per minute for the first four minutes and then rose to 9.09 grams for the remaining six minutes of the immersion. When the left hand was now put into cold water the flow in the right was cut down to 3.9 grams per 100 c c per minute for the first three minutes and then increased (for the remaining five minutes) to 10.14 grams per 100 c c per minute. The vasomotor reaction to cold accordingly, although initially intense, was not especially persistent, giving way to a marked vasodilatation while the contralateral hand was still in the cold water.

The effect of certain poisons on the vasomotor reflexes, as investigated by this method, seemed sufficiently definite to be worthy of mention.

TABLE 27—CALORIMETRIC MEASUREMENTS IN CASE OF MRS. X

Time	Right	Left	Room	Time	Right	Left	Room
3 07	29 965	29 97	27 2	3 25		30 925	27 3
3 09	29 995	30 03		3 26		30 99	
3 10	30 03	30 07		3 27		31 03	
3 11	30 09	30 13		3 28		31 11	
3 12	30 16	30 205		3 29		31 155	
3 13	30 25	30 26	27 3	3 30		31 20	
3 14	30 33	30 34		3 31		31 24	
3 15	30 45	30 45		3 32		31 27	
3 16	30 525	30 53		3 33		31 33	27 4
3 17	30 605	30 625		3 34		31 42	
3 18	30 68	30 68		3 35		31 50	
3 19	30 72	30 73*		3 36		31 60	
3 20	30 755	30 755		3 37		31 655	
3 21	30 795	30 79		3 38		31 71	
3 22		30 805		3 38½		31 74	
3 23		30 82		3 48	30 625		27 3
3 24		30 85		3 48½		31 675	

* Here she began to get nervous about the cold water which she saw in preparation being cooled by ice.

Cooling of calorimeters, R, 0.17 C in twenty-seven minutes, L, 0.065 C in ten minutes. Volume of right hand 317 c c, of left hand 326 c c.

Mrs. X, aged 48, height 4 feet, 10 inches, weight 118 pounds, was admitted at the dispensary May 11, 1911, complaining of a cough that she had had for a week. Her general health was undisturbed. She had had no children but

eight miscarriages. She was obviously under the influence of alcohol, and for this reason the blood flow in the hands was examined.

The hands were in bath at 2 59 p m, in calorimeters at 3 08. At 3 21 the right hand was put into water at 8 4 C. At 3 30 the right hand was put into water at 43 C. At 3 38½ the left hand was taken out of the calorimeter. Mouth temperature 37 35 C. Pulse 96.

The initial flow in this case was good (13 05 grams per 100 c c per minute for the right hand and 12 03 grams for the left), even for the relatively high room temperature (27 3 C). The flow in the left hand was diminished to 4 6 grams when the right was immersed in cold water. After three minutes the vasoconstriction gave place to vasodilatation, the flow increasing to 11 08 grams for the remaining six minutes of immersion of the right hand in cold water. On immersing the right hand in warm water the flow in the left sank to 7 52 grams per 100 c c per minute (for three minutes) and then increased to 15 92 grams per 100 c c per minute for the remaining five and one-half minutes of immersion, an exceptionally large increase on the top of the good initial flow. The suggestion is that the influence of the alcohol favors reflex vasodilatation of the cutaneous vessels. Evidence of this has also been secured in other cases.

In a case of lead poisoning with no symptoms of peripheral neuritis (John K.) the opposite result was obtained, good crossed vasoconstriction but practically no increase of the initial flow. In other words, the vasomotor mechanism, which under the influence of alcohol was exceptionally ready to respond to appropriate stimuli by vasodilatation, tended, under the influence of lead poisoning, to respond especially to stimuli causing vasoconstriction. In accordance with this the blood pressure was high in John K. (180 mm Hg). There was no decided anemia and the flow in the hands before the vasomotor reactions were tested was within the normal range (8 96 grams per 100 c c per minute for the right hand and 8 81 grams for the left, with room temperature 23 C).

John K., a laborer, aged 52, was admitted to the City Hospital, May 13. He worked in an automobile factory scraping paint from wheels. For two weeks he had been constipated, with intense pain in the abdomen and the occurrence of vomiting. A lead line was noted on the gums. The lips were red. A blood count showed erythrocytes 4,080,000, leukocytes 6,800. Knee-jerks were present and equal. The grip of the hands was not noticeably weakened. The pupils reacted to light and accommodation. The radial pulse was regular and of high tension. There was some fibrosis of the artery. He was discharged improved on May 25. The blood flow in the hands was examined May 14. He works best with his left hand though he eats and writes with the right.

The hands were in bath at 1 43 p m, in calorimeters at 1 55½. At 2 09 the left hand was put into water at 8 C. At 2 20 the left hand was put into water at 43 2 C. At 2 33 the right hand was taken out of the calorimeter.

TABLE 28—CALORIMETRIC MEASUREMENTS IN CASE OF JOHN K

Time	Right	Left	Room	Time	Right	Left	Room
1 55	31 00	30 87		2 16	31 895		
1 57	31 07	30 94		2 17	31 925		22 3
1 58	31 12	31 00		2 18	31 97		
2 00	31 21	31 08		2 19	31 99		
2 01	31 27	31 15		2 20	32 02		
2 02	31 33	31 21	23 2	2 21	32 05		
2 03	31 39	31 27		2 22	32 075		22 3
2 04	31 45	31 33		2 23	32 10		
2 05	31 50	31 39		2 24	32 125		
2 06	31 56	31 44	23 0	2 25	32 16		
2 07	31 62	31 50*		2 26	32 21		
2 08	31 65	31 53		2 27	32 25		22 3
2 09	31 68	31 56		2 28	32 295		
2 10	31 71			2 29	32 32		
2 11	31 72			2 30	32 36		
2 12	31 735			2 31	32 395		22 3
2 13	31 78		22 4	2 32	32 435		
2 14	31 81			2 33	32 48		22 4
2 15	31 87			2 46	32 29	31 10	

* Here he saw ice brought and put into the cold water and seemed to become apprehensive

Cooling of calorimeters, R, 0.19 C in thirteen minutes, L, 0.46 C in thirty-seven minutes. Volume of right hand 475 cc, of left 472 cc. Water equivalent of calorimeters with contents, R, 3,475, L, 3,473. Pulse 108.

In another case of lead poisoning (S), a man aged 40, the flow was 8.05 grams in the right and 8.74 grams in the left hand with room temperature 21.8 C. In this case also the tendency to reflex vasoconstriction was decided, as will be seen by referring to the general table of results.

TABLE 29—CALORIMETRIC MEASUREMENTS IN CASE OF S

Time	Right	Left	Room	Time	Right	Left	Room
3 40	30 03	30 13		3 58	31 11		
3 41	30 10	30 20	21 9	3 59	31 12		
3 42	30 16	30 26		4 00	31 15		
3 43	30 20	30 32		4 01	31 17		
3 44	30 28	30 39		4 02	31 18		21 7
3 45	30 335	30 45	21 8	4 03	31 195		
3 46	30 40	30 53		4 04	31 26		
3 47	30 495	30 625		4 05	31 31		
3 48	30 58	30 71		4 06	31 375		22 9
3 49	30 63	30 79		4 07	31 42		
3 50	30 66			4 08	31 47		
3 51	30 69			4 10	31 53		
3 52	30 72			4 11	31 57		
3 53	30 78		21 9	4 12	31 60		22 8
3 54	30 86			4 13	31 64		
3 55	30 91			4 14	31 695		
3 56	31 00			4 27	31 53	30 37	22 5
3 57	31 07		21 5				

Cooling of calorimeters, R, 0.165 C in thirteen minutes, L, 0.42 C in thirty-eight minutes. Volume of right hand 527 cc, of left hand 521 cc. Rectal temperature 38.05 C.

S, a painter, aged 40, height 5 feet, 8½ inches, was admitted to the City Hospital, March 31. He complained of colic, and a blue line was noted around his gums. He had been ill two or three months, and although weak was considerably better. He had no wrist-drop. He was discharged improved April 15. The blood flow in the hands was examined on April 3. Hands were in bath at 3.29 p m, in calorimeters at 3.39. At 3.49 the left hand was put in water.

at 8 C He felt it very cold At 4 01 p m the left hand was put into water at 43 C At 4 09 left hand dried and wrapped At 4 14 the right hand was taken out of calorimeter Pulse 120

In Roderick D, a blacksmith, aged 27, excessively addicted to cigaret smoking from boyhood, the flow in the hands was large (12 77 grams for the right and 12 38 grams for the left hand per 100 c c per minute, with the rather high room temperature of 26 2 C) Immersion of the left hand in cold water caused a transient vasoconstriction of the right, the flow falling to 7 73 grams for the first two minutes of immersion to rise again to 11 03 grams per 100 c c per minute for the remaining nine minutes, during which the left hand continued in the cold water Warm water caused only a small preliminary vasoconstriction, the flow then increasing again though not quite to the high initial value Scratching the skin with a blunt point caused a well-marked red line which persisted for a considerable time In this case everything points to the existence of a tendency to vasodilatation, which is in agreement with the observation that nicotine after a preliminary excitation causes depression of the sympathetic nerve cells

Examination of flow in hands of Roderick D Hands in bath at 2 35½ p m, in calorimeters at 2 47¼ At 2 59 the left hand was put into water at 8 C He felt it very cold At 3 10½ p m the left hand was put into water at 43 5 C At 3 21 right hand was taken out of calorimeter

TABLE 30—CALORIMETRIC MEASUREMENTS IN CASE OF RODERICK D

Time	Right	Left	Room	Time	Right	Left	Room
2 46½	29 88	29 84		3 06	31 70		
2 48	29 96	29 91		3 07	31 76		
2 49	30 07	30 04	26 2	3 08	31 83		
2 50	30 19	30 20		3 09	31 90		26 3
2 51	30 30	30 31		3 10	31 99		
2 52	30 435	30 44	26 15	3 11	32 06		
2 53	30 565	30 54		3 12	32 11		
2 54	30 65	30 61		3 13	32 17		
2 55	30 78	30 72	26 2	3 14	32 20		
2 56	30 87	30 81		3 15	32 27		
2 57	31 01	30 90		3 16	32 33		
2 58	31 09	30 98	26 3	3 17	32 39		
2 59	31 19	31 065		3 18	32 46		26 4
3 00	31 24			3 19	32 52		
3 01	31 30			3 20	32 56		
3 02	31 37			3 21	32 63		26 5
3 03	31 46			3 22		30 89	
3 04	31 56		26 4	3 34	32 50		
3 05	31 63						

Cooling of calorimeters, R, 0 13 C in thirteen minutes, L, 0 175 C in twenty-three minutes Volume of right hand 535 c c, of left hand 513 c c Water equivalent of calorimeters with contents, R, 3,523, L, 3,505 Mouth temperature 37 4 Pulse 84

The last case to be cited is that of a young man who shot himself through the brain

Andrew K, a young foreign laborer, was brought to the City Hospital by the police on May 16, at 4 45 p m, with a crescent-shaped wound in the scalp on the left side not far from the median line, midway between the glabella and

TABLE OF RESULTS OF CALORIMETRIC MEASUREMENTS IN TWENTY-ONE CASES

Case	Age	Date	Pulse Rate	Temperature (C) of			Volume of Part in cc		Heat Given Off in Gm Calories		Blood Flow in Gm per Min		Flow per 100 cc of Part per Min		Notes		
				Arterial Blood	Calorimeters		Right	Left	Right	Left	Right	Left	Right	Left			
					Room	Right										Left	
Kaspar J	50	5/ 5/11	92	24.2 24.2 24.4 24.4 25.3 25.4 25.4 25.3 25.3	36.70	29.79 30.05 30.20 30.33 30.20 30.39 30.50 30.60 30.69	29.66	511	457	1,121 1,121 210 1,051 1,511 299 790 221 597	830	8	22.54 26.76 17.95 26.19 18.45 13.16 20.22 13.44 18.40	16.38	4.80 5.69 3.82 5.55 3.76 2.68 4.12 2.74 3.75	3.53	Brachial neuritis (rt) Hands Left hand in water at 43 O Left hand in water at 95 O Left hand still in cold water Hands Left hand in water at 42.6 O Left hand still in warm water Left hand in water at 82 O Left hand still in cold water
John McH	53	6/ 5/12 6/ 6/12	88	23.3 23.3 22.9 23.0	37.15 37.00	31.10 31.66 31.91 32.03	31.04 31.54	494 512	476 491	2,199 2,418 455 981	1,947 2,058	19 18 6 7	21.25 27.95 16.55 31.33	18.63 23.26	4.30 5.46 3.23 6.11	3.91 4.74	Hands Left hand in water at 43 O Left hand still in warm water
Frank S	64	4/23/12	96	21.0 21.3 22.1 22.9	36.70	29.46 29.16 31.09 31.13	29.35 29.16 31.09 31.19	1,020	950	210 756 1,304	414 280 755 1,510	14 10 8 12	2.30 4.12 17.92 20.39	4.47 4.12 18.36 23.57	0.22 0.43 4.20 4.82	0.47 0.43 4.39 5.57	Feet Right foot in water at 41 O Hands Hands
Chas deM	23	7/10/12 (Blood pressure, 121 74)	68	30.1 29.9 29.8 29.8 29.7 25.1 24.0	37.00	31.85 32.41 32.61 32.81 33.01 31.67 31.02	31.83 32.41 32.61 32.81 33.01 31.67 31.02	488	479	3,380 347 1,253 313 1,357 2,303 1,581	3,565 347 1,253 313 1,357 2,303 2,097	15 3 7 2 2 11 22	48.61 23.00 9.45 41.50 53.99 47.53 12.90	51.57 23.00 45.30 41.50 53.99 42.06 17.40	9.96 5.84 9.45 8.63 11.27 8.95 0.90	10.76 5.84 9.45 8.63 11.27 8.95 1.20	Alcoholic neuritis Hands Right hand in water at 81 O Right hand still in cold water Right hand in water at 43.1 C Right hand still in warm water Allowing for swelling left hand Feet
Frank D	39	7/23/12 (Blood pressure, 133 86)	76	25.2 25.1 25.1 25.2 25.2	37.10	31.68 32.01 32.14 32.38 32.63	31.55 32.01 32.14 32.38 32.63	572	542	3,126 670 1,200 390 1,886	3,141 670 1,200 390 1,886	11 5 6 5 8	58.25 29.25 44.80 18.36 53.60	57.16 29.25 44.80 18.36 53.60	10.18 5.40 8.26 3.38 10.81	10.54 5.40 8.26 3.38 10.81	Left wrist drop (pressure) Right hand in water at 8 O Right hand still in cold water Right hand in water at 43 O Right hand still in warm water
Stanislas O	32	4/19/11	72	23.7 23.7 23.6 23.6 23.7 23.5	36.8	30.16 30.46 30.69 30.89 31.39 31.68	29.91	486	442	1,220 871 766 1,568 1,463 731	242	6 4 3 6 6 3	34.02 33.17 46.42 49.93 50.08 52.89	6.50	7.0 7.85 9.55 10.23 10.30 10.83	1.47 7.85 9.55 10.23 10.30 10.83	Hands Left hand in water at 12 O Left hand dried and wrapped Left hand in water at 43.5 O Left hand in water at 9 O Left hand dried and wrapped
Mrs Eva M	56	4/16/12	101	23.0	37.45	30.75	30.58	334	328	2,286	1,611	18	21.06	11.47	6.30	4.39	Left hemiplegia Hands
George H	40	7/18/12 (Blood pressure, 91 83)	69	26.5 26.7 26.4 26.4 25.5 24.7	36.95	31.76 32.01 32.17 32.41 31.65 31.06	31.96	161	500	1,889 312 1,109 1,126 2,421 1,335	2,601	12 3 7 10 12 12	33.70 23.39 36.82 27.55 42.70 21.16	19.10	7.26 5.04 7.93 5.94 9.38 1.63	9.82	Right hemiplegia Hands Left hand in water at 8 O Left hand still in cold water Left hand in water at 43 O Hands Feet

* The tabular summary of results on A O H, Casimir M, John S, Mrs M O, Max B, Mrs Mary N, O and Abe K is given in Table II, Heart, 1911, III, 84

Dennis H	41	4/11/12 (Blood pressure, 118)	80	25 5	36 8	30 04	30 06	505	451	1,995	1,590	17	21 17	16 02	1 19	3 75	Left hemiplegia For the first six minutes Right hand in water at 8 O Right hand still in cold water Right hand in water at 43 O Right hand still in warm water
				25 5		30 47	30 51			490	276	6	11 33	8 13	2 84	1 80	
				25 4			30 37				588	7		15 74		3 49	
				25 4			31 03				967	7		26 60		5 00	
				25 4			31 18				484	4		23 92		5 30	
Joseph S	54	8/ 7/12	124	25 4			31 33				967	8		21 55		5 51	Feet Tables Hands Left hand put in water at 8 4 O Left hand still in cold water Left hand in water at 42 8 O Left hand still in warm water
				25 0	37 75	31 12	31 14	1,110	1,104	504	686	12	8 30	9 61	0 76	0 88	
				25 0	37 85	31 43	31 30	425	441	1,872	1,465	13	24 02	10 11	5 86	1 33	
				25 0		31 68				492		4	22 15		5 21		
				25 0		31 83				1,002		8	23 11		5 43		
W B O	57	11/11/14	84	25 0		32 00				584		5	22 18		5 22		Feet Tables Hands Left foot in water at 44 1 O Hands Left hand in water at 115 O Left hand still in warm water Left hand in water at 13 O Left hand still in cold water
				25 2		32 12				721		6	23 30		5 48		
				21 5	36 30	30 08	31 02	925	943	384	624	16	5 01	8 27	0 54	0 87	
				21 8		30 85				413		12	7 01		0 75		
				22 9	36 40	31 82	31 31	380	388	860	810	10	20 02	10 60	5 42	5 05	
Gabriel M	41	11/17/14 11/19/14	92 100	22 9		31 88				310		5	15 21		4 01		Feet Hands Left hand in water at 43 O Right foot in water at 43 5 O Hands Feet Right foot in water at 43 O Right foot still in warm water Right foot in water at 8 7 O Right foot still in cold water
				22 9		31 95				845		9	23 44		6 16		
				22 8		32 01				49		1	12 40		3 26		
				22 8		32 05				631		8	20 14		5 30		
				22 6													
John M	45	12/ 3/14	108	22 6	36 76	31 50	31 50	431	395	390	491	19	4 33	5 14	1 00	1 37	Tables Hands Left hand in water at 43 O Feet Right foot in water at 43 5 O Hands Feet Right foot in water at 43 O Right foot still in warm water Right foot in water at 8 7 O Right foot still in cold water
				23 9	36 70	31 74	31 64	424	407	827	797	15	12 35	11 66	2 91	2 86	
				24 3		31 79				577		10	13 05		3 07		
				22 8	36 60	31 18	31 12	1,117	1,092	369	404	12	6 30	6 82	0 56	0 62	
				23 0			30 99				1,085	22		9 76		0 89	
Joseph K	48	11/24/14	108	23 0		31 36				478		8	11 79	11 25	2 77	2 83	Tables Feet Right foot in water at 8 O Left hand in water at 8 O Left hand still in cold water Left hand in water at 43 1 O Feet Right foot in water at 8 3 O Hands Left hand in water at 8 4 O Left hand in water at 43 O Left hand still in warm water Right foot in water at 43 O
				22 1	37 05	31 42	30 94	425	390	806	461	11	10 53	7 08	0 96	0 73	
				22 2	36 95	30 88		1,092	1,087			4		7 09		0 65	
				22 5			30 88				155	1		10 05		0 92	
				22 6			30 86				551	10		9 18		0 81	
John M	45	12/ 3/14	116	22 8		30 84				202		4		7 60		0 70	Tables Feet Right foot in water at 9 5 O Right foot in water at 42 6 O Right foot still in warm water Hands Left hand in water at 8 O Left hand still in cold water Left hand in water at 43 1 O Feet Right foot in water at 8 3 O Hands Left hand in water at 8 4 O Left hand in water at 43 O Left hand still in warm water Right foot in water at 43 O
				23 0		30 80					121	10					
				24 2	37 05	31 46	31 52	1,067	1,042	960	936	14	13 62	13 13	1 27	1 28	
				24 6			31 55				592	12		9 95		0 95	
				24 8			31 57				247	4		12 52		1 17	
Joseph K	48	6/26/12	96	24 9			31 63				839	10		17 20		1 65	Tables Feet Right foot in water at 9 5 O Right foot in water at 42 6 O Right foot still in warm water Hands Left hand in water at 8 O Left hand still in cold water Left hand in water at 43 1 O Feet Right foot in water at 8 3 O Hands Left hand in water at 8 4 O Left hand in water at 43 O Left hand still in warm water Right foot in water at 43 O
				24 9			31 63					8	28 14	30 22	6 60	7 57	
				24 2	37 15	31 90	31 62	426	399	1,065	1,160	5	27 46		6 16		
				24 2		32 06				629		5	36 09		8 47		
				24 5		32 20				804		9	37 15		8 79		
Joseph K	48	6/26/12	96	24 5		32 43				1,432		9	37 15		8 79		Tables Feet Right foot in water at 9 5 O Right foot in water at 42 6 O Right foot still in warm water Hands Left hand in water at 8 O Left hand still in cold water Left hand in water at 43 1 O Feet Right foot in water at 8 3 O Hands Left hand in water at 8 4 O Left hand in water at 43 O Left hand still in warm water Right foot in water at 43 O
				24 7	37 05	31 98	32 06	1,006	1,001	621	706	10	13 60	15 72	1 35	1 57	
				24 7			32 05				880	11		13 96		1 39	
				27 3	37 05	31 44	31 43	495	479	2,234	2,121	10	44 24	41 93	8 04	8 75	
				27 3		31 88				1,309		10	28 13		5 68		
Joseph K	48	6/26/12	96	27 5		32 16				1,187		7	38 53		7 78		Tables Feet Right foot in water at 9 5 O Right foot in water at 42 6 O Right foot still in warm water Hands Left hand in water at 8 O Left hand still in cold water Left hand in water at 43 1 O Feet Right foot in water at 8 3 O Hands Left hand in water at 8 4 O Left hand in water at 43 O Left hand still in warm water Right foot in water at 43 O
				27 5		32 42				977		4	58 61		11 84		
				26 4	36 95	31 05	30 99	1,280	1,292	537	586	16	6 31	6 85	0 50	0 51	
				26 4			30 98			537		10		6 75		0 53	
				26 7							363						

TABLE OF RESULTS OF CALORIMETRIC MEASUREMENTS IN TWENTY-ONE CASES—(Continued)

Case	Age	Date	Pulse Rate	Temperature (C) of			Volume of Pant in c c		Heat Given Off in Gm Calories		Blood Flow in Gm per Min	Flow per 100 c c of Pirt per Min	Notes
				Room	Arterial Blood	Glomerometers	Right	Left	Right	In Mins	Right	Left	
Fred L.	22	11/18/12	88	22.0	37.2	30.56	30.57	377	1,626	13	29.93	18.09	Cerebral tumor Hands
						30.75			187	2	16.10		Left hand in water at 13 O
						30.97			1,787	10	31.87		Left hand still in warm water
				22.8		31.19			285	6	8.78		Left hand in water at 11.2 O
				22.3		31.25			599	6	18.64		Left hand still in cold water
J S.		11/20/12	100	21.4	37.25	31.35	31.33	380	1,652	13	23.93	20.87	Hands
				20.9		31.48			320	3	12.51		Right hand in water at 43 O
				20.7		31.65			1,396	8	34.62		Right hand still in warm water
				20.7		31.80			747	11	13.84		Right hand in water at 10.5 O
				20.7		31.91			1,179	11	22.30		Right hand in water at 43 O
Mrs X.	48	4/ 5/12	92	25.9	37.3	30.60	30.64	358	749	6	20.70	22.55	Tetanus Hands
				26.2		30.71			307	4	12.94		Left hand in water at 43.5 O
				26.0		30.90			1,226	6	35.47		Left hand still in warm water
				26.0		31.08			255	3	15.18		Left hand in water at 7 O
				25.8		31.24			1,073	5	39.34		Left hand still in cold water
John K.	52	5/11/11	96	27.3	37.35	30.44	30.46	326	2,579	10	41.47	39.23	Alcoholic intoxication Hands
				27.3		30.82			263	3	15.22		Right hand in water at 8.4 O
				27.3		31.05			1,309	6	38.48		Right hand still in cold water
				27.4		31.27			403	3	24.57		Right hand in water at 43 O
						31.54			1,493	5½	51.92		Right hand still in warm water
S.	40	5/14/12 (Blood pressure, 180)	108	23.0	37.2	31.38	31.25	472	2,676	12	42.57	41.61	Lead poisoning Hands
				22.4		31.71			313	3	21.11		Left hand in water at 8 O
				22.3		31.88			1,390	8	36.29		Left hand still in cold water
				22.3		32.07			556	4	30.10		Left hand in water at 43.2 O
				22.3		32.30			1,702	9	42.88		Left hand still in warm water
Roderick D.	27	4/ 3/12	120	21.8	37.6	30.33	30.46	527	2,497	9	42.40	45.54	Lead poisoning Hands
						30.68			440	3	23.55		Left hand in water at 8 O
				21.9		30.92			1,635	6	45.33		Left hand still in cold water
				21.5		31.14			235	3	19.21		Left hand still in cold water
				21.7		31.18			176	2	15.23		Left hand in water at 43 O
Andrew K.	27	5/10/11	84	22.9		31.35			1,372	6	40.65		Left hand still in warm water
				22.8		31.60			879	5	32.55		Left hand dried and wrapped
				26.2	37.1	30.58	30.49	513	4,615	11	68.35	63.54	Tobacco Hands
				26.3		31.25			158	2	41.37		Left hand in water at 8 O
				26.4		31.65			2,748	9	59.00		Left hand still in cold water
Andrew K.		5/17/12 6/ 6/12	80 112	26.4		32.10			880	4	46.12		Left hand in water at 43.5 O
				26.4		32.42			1,762	7	53.16		Left hand still in warm water
				23.5	37.25	31.54	31.50	463	2,687	11	47.53	39.66	Bullet wound of brain Hands
				23.0	38.15	31.95	32.09	460	1,615	10	23.94	38.10	Blood pressure 132

occipital protuberance The patient appeared to be in stupor, he did not talk The right pupil was larger than the left and its outline was irregular The pupils reacted to light The external rectus of the right eye was paralyzed Blood was flowing from the nostrils, but no abrasions were visible in the interior The tongue protruded in the median line On the hard palate was a blackish discoloration covering a bullet hole (It was elicited afterwards that he had shot himself with a revolver) There was no paralysis, the reflexes were normal The rectal temperature was 98.8 F The spinal fluid from the lumbar puncture was bright red, containing much blood It flowed 120 drops per minute May 17 the eye grounds were normal The systolic blood pressure was 140 He voided urine involuntarily He did not speak, although he was perfectly conscious There was no Babinski sign The temperature was 99.8 F at 8 a m, and the same at noon On May 18 he voided urine, the systolic blood pressure was 120 From May 19 to May 21 his condition was the same On May 24 the systolic pressure was 126, on June 6, 132

The blood flow in the hands was examined on May 17 and again on June 6 At the first examination he sat quite well in the chair, but was absolutely silent Hands in bath at 3.05 p m, in calorimeters at 3.14½, out of calorimeters at 3.28 Pulse 80 (lying down) Room temperature 23.4 C He kept clutching the stirring feathers occasionally

TABLE 31—CALORIMETRIC MEASUREMENTS IN CASE OF ANDREW K

Time	Right	Left	Room	Time	Right	Left	Room
3 14	31.17	31.17		3 23	31.61	31.52	
3 17	31.22	31.23		3 24	31.64	31.59	
3 18	31.28	31.26		3 25	31.70	31.63	
3 19	31.33	31.33		3 26	31.77	31.70	
3 20	31.39	31.36		3 27	31.81	31.72	
3 21	31.45	31.43		3 28	31.87	31.76	
3 22	31.55	31.52		3 43	31.69	31.59	

Cooling of calorimeters in fifteen minutes, R, 0.18 C, L, 0.17 C Volume of right hand 466 cc, of left 463 cc Water equivalent of calorimeters with contents, R, 3,468, L, 3,465 Rectal temperature 37.75 C

Second examination of Andrew K, June 6 So far he has recovered without symptoms The right pupil reacts to light equally with the left and now there is little difference in size The right external rectus is still paralyzed He will now talk freely Rectal temperature 38.65 C Pulse (sitting) 112 Pulse not large Hands in bath at 1.44 p m

TABLE 32—CALORIMETRIC MEASUREMENTS IN SECOND EXAMINATION OF ANDREW K

Time	Right	Left	Room	Time	Right	Left	Room
1 54	31.68	31.67		2 05	31.93	32.07	23.0
1 56	31.66	31.67		2 06	31.965	32.12	
1 57	31.68	31.70	22.8	2 07	31.99	32.155	
1 58	31.70	31.74		2 08	32.02	32.19	23.1
1 59	31.72	31.77	22.8	2 09	32.05	32.23	
2 00	31.74	31.825		2 10	32.08	32.27	23.0
2 01	31.78	31.86		2 11	32.11	32.325	
2 02	31.81	31.92		2 19	32.00		
2 03	31.865	31.97	22.85	2 19½		32.205	
2 04	31.895	32.025					

Cooling of calorimeters, R, 0.11 C in eight minutes, L, 0.12 C in 8½ minutes Volume of right hand in calorimeter 472 cc, of left 460 cc Water equivalent of calorimeters with contents, R, 3,473, L, 3,463

The patient was discharged cured. He was readmitted July 31 suffering from rheumatism and chronic alcoholism and was discharged "improved" on August 27.

At the first examination of Andrew K., made not much more than twenty-four hours after he was brought into the hospital, the blood flow in the right hand was 10.20 grams per 100 c.c. per minute and in the left 8.56 grams, with room temperature 23.5 C. At the second examination, nearly three weeks later, the flows were 6.13 grams and 8.28 grams respectively for the right and left hands, with room temperature 23 C. He had some fever at the time of the second examination which is perhaps associated with the somewhat smaller flows.¹¹ It will be noted that on both occasions a distinct difference existed in the rate of flow in the two hands. The fact that there is no constancy in this difference, the greater flow being in the right hand at the first examination, in the left hand at the second, indicates that the differences are of vasomotor origin, but it is impossible to say whether they are related in any way to the brain injury. Our observations on chronic alcoholism, for which in the sequel this man was again admitted to the hospital, would perhaps suggest this rather than the brain lesion as the condition associated with the vasomotor instability. There is, of course, no obvious reason why a bullet wound through a cerebral hemisphere which occasioned no paralysis should cause a permanent difference of flow between the hands, nor indeed any obvious reason why so long as it was not associated with general symptoms it should produce any effect whatever on the circulation in the extremities. As a matter of fact, the average hand flows at the two examinations are quite within the normal range.

SUMMARY

1. In early unilateral brachial neuritis the blood flow in the affected hand was found to be decidedly greater than in the normal hand. This is interpreted as due to partial paralysis of the vasoconstrictor fibers in the nerves involved in the pathologic process.

In long-standing unilateral neuritis with decided atrophy of the affected part, the blood flow is less on the side of the lesion than on the normal side. There is some evidence that one factor in the diminution of the flow may be a change in the walls of the arteries consequent on the injury to the vasomotor nerves, which leads to diminution of the lumen. This may be considered an adaptive change correlated with the diminished function of the part. The diminution in the flow may also be due to the regaining of vascular tone by the paralyzed part, even in the absence of regeneration of its nerve supply.

¹¹ Jour. Exper. Med., 1913, XVIII, 372.

In peripheral neuritis affecting mainly muscular nerves, the changes in the blood flow of the hands and feet are not so conspicuous, as when the cutaneous nerves are also involved, since a large portion of the total flow in these parts must belong to the skin

2 In hemiplegia there is, in general, a marked deficiency in the blood flow in the paralyzed members. Considerable differences, however, exist in different cases in this regard, and also in the extent to which the vasomotor reflexes from the normal to the paralyzed part are affected. Whether these differences depend at all on the position of the lesion or are associated with the duration and completeness of the paralysis has not been determined. There is some evidence that reflex vasoconstriction is more easily produced in the paralyzed parts than reflex vasodilatation.

3 In tabes, the blood flow in both hands and feet, but especially in the feet, has been found decidedly subnormal and the vasomotor reflexes feeble.

4 In lead poisoning (without paralysis), the tendency to reflex vasoconstriction was conspicuous. This seemed to be the case also in alcoholic neuritis. In alcoholic intoxication and in a case of excessive cigaret smoking, the opposite was observed, namely, a tendency to marked reflex vasodilatation.

5 It is suggested that, in some cases, examination of the blood flow might aid in the detection of malingering, when the attempt is made to simulate certain neuropathologic conditions. It seems probable that the differential diagnosis, for instance, between such conditions as cerebral hemorrhage and alcoholic intoxication, or between hysterical palsy and paralysis due to an organic lesion, in doubtful cases might be facilitated by blood-flow measurements.

I wish to express my obligations to the staffs of the City Hospital and of Lakeside Hospital for aid without which this investigation could not have been carried out.

TUMORS OF THE SYMPATHETIC NERVOUS SYSTEM AND THE MEDULLA OF THE ADRENAL GLANDS, ESPECIALLY MALIGNANT NEUROBLASTOMA

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The morphology and still more the etiology of tumors is as yet an unfinished chapter. Fifty years have elapsed since R. Virchow (1863-1865) published his epochmaking work *Die Krankhaften Geschwulste* and thereby founded the morphology of most of the now well-known species of tumors.

Since then a number of prominent scientists have used the time well. I will mention only Ribbert and his numerous contributions to the subject of tumors. But still new forms are discovered or formerly not well understood forms are reclassified. Such is the case with regard to the group of neoplasms this paper is to discuss—certain tumors of the nervous system and of the adrenal glands. These peculiar growths have formerly been classified as sarcoma, the storeroom containing so many incongruous matters which need a thorough putting to right. This process is, however, progressing, as pathologic new formations which prove to be of an inflammatory nature, for example, the lymphogranuloma or independent species of tumors which according to their structure and genesis should have been excluded from the ordinary forms of sarcoma, are being separated.

It is a well-known fact that tumors may originate from and consist of elements of nervous tissue. Best known are the not infrequent and important glioma of the central nervous system and of the retina. The so-called neurofibroma occurs frequently. Of especially great interest from a general pathologic and clinical point of view are the multiple growths of this kind, the multiple neurofibroma with its many different forms. I have in an earlier paper gone more thoroughly into this matter¹. The origin of neurofibroma is generally conceded to be the connective tissue of the nerve trunks, but this is as yet not universally accepted, as certain authors (Verocay, Herxheimer) doubt this theory and maintain that the cells of the sheath of Schwann form the matrix. As these cells are supposed to belong to and originate from the nervous system the new growths arising from them would

¹ Harbitz, Francis. Multiple Neurofibromatosis (von Recklinghausen's Disease), *THE ARCHIVES INT. MED.*, 1909, **111**, 32.

be of ectodermal origin and would be classified with glioma. These different opinions are not yet settled.

Another tumor is described and a separate place claimed for it, namely the ganglioneuroma, a tumor containing ganglion cells and nerve fibers, a genuine neuroma in distinction from the just mentioned "pseudoneuroma." The existence of such tumors has been maintained from Virchow's time, but the reports have not gained absolute confidence, these tumors are considered very rare. Personally, I have never seen an assuredly certain case of ganglioneuroma if as such are not classified the nodes found in nodular sclerosis of the brain. In recent years new observations have shed light on this subject, and as a result of newer and better methods of differentiation of the component tissues of the nervous system it now may be safely assumed that ganglioneuroma does occur but seldom and then often in varying morphologic forms.

J. H. Wright has shown conclusively that certain peculiarly constructed tumors arise from the sympathetic nervous system and from the medullary portion of the adrenal glands. These tumors consist of immature and undifferentiated nerve tissue of a characteristic structure and are eminently malignant in their development and course.

It will be well to review the embryologic origin of the sympathetic system² in order to understand the development and structure of these neoplasms.

The adrenals are developed from a divided source. Their cortical portion comes into existence as early as the fourth week of fetal life, supposedly from a thickening of the celomic mesothelium, and becomes merged into a joint organ, the mesonephros, which may be easily recognized in the eighth week. If this persists it results in the permanent union of the cortices of both adrenals as well as in the occurrence of accessory (supernumerary) adrenals in other locations, which all consist of cortex although often somewhat abnormal in structure. From such cortical remnants are developed the so-called "hypernephromas," one of the most frequent neoplasms of the kidneys, a genuine ectodermal and epithelial growth.

The medulla is derived from the sympathetic system whose elements travel into the cortical portion and subsequently aggregate in its center. To this fact is due the close relation between the adrenals and the sympathetic system. The primary formative cells of the medulla, the mother cells of the sympathetic ("sympathogonies"), are small cells with few fibers and intensely colored nuclei. They are numerous, lymphocyte-like, with sparse protoplasm, and give no reaction with the chrome salts.

² Based on the work of Kohn.

Later, during the third and fourth month, the cells differentiate into (a) sympathetic ganglion cells with fibers, (b) into larger cells containing large clear nuclei, polymorphous, cylindrical and epithelium-like, often arranged in bands. Their protoplasm and to some extent their nuclei give fine brown to greenish granulations with chrome solution so that microscopically the tissue appears brown. These cells are consequently named chromaffin, chromaphil or facochrome cells.

Such chromaffin, epithelium-like cells are also found scattered among the ganglion cells and fibers and are found in heaps in certain locations as in the carotid ganglion (about the size of a pea, at the bifurcation of the common carotid) which also contains ganglion cells and nerve fibers. They are found in the organ of Zuckerkandl, especially prominent in fetal life and newborn children, a flat body from 3 to 20 mm long, situated on the anterior aspect of the aorta, around the inferior mesenteric artery. This organ contains as a rule no ganglion cells. Finally they are found in the coccygeal ganglion, a simple, nearly pea-sized organ on the anterior lip of the coccyx. These larger accumulations of chromaffin cells are also named paraganglia, and all chromaffin tissue collectively, the chromaffin system.

This system arises then from the sympathetic nerve and this large, widely branching nerve has its origin, partly from motor nerves of the spinal cord, partly from the spinal ganglia, and it contains primarily fibers and cells—"neuroblasts"—in groups, the first formation of the sympathetic ganglia. The paraganglia, hence, are only a part of those migrated cells and fibers endowed with special differentiation and have their ultimate origin in the ectodermal tissue. Kohn maintains that heaps of undifferentiated embryonic nerve cells, "neurocytes," may be retained here and there in the nerves in a latent condition, later to take on renewed activity and develop into tumors of various kinds.

Tumors arising from the adrenal medulla or from the sympathetic system, collectively termed neuroblastomas, as we now know may be very differently constructed. This is due to various stages of development in which the cells giving rise to the tumor were at that particular time. Schematically we may have 1 Tumors consisting of fully differentiated nerve tissue with ganglion cells and nerve fibers, usually termed ganglioneuroma or genuine neuroma. 2 Tumors made up of chromaffin cells in the sympathetic or parasympathetic tissues termed paraganglioma, mostly of an epithelial nature. 3 Tumors composed of undifferentiated sympathetic formative cells, the so-called malignant neuroblastoma, relatively frequent and important growths, whose real nature first has been understood in recent years.

Transitional as well as mixed forms are encountered as might be expected from the manner in which the sympathetic system and the

adrenal medulla are developed. It also appears as if the mixed forms occur more frequently than formerly supposed (Landau, Martins, Wahl). All three forms may be found combined in the same tumor or in the same individual (Landau's case³ and particularly a case described by Wahl⁴ of three primary lesions in a 1½ year old child). Besides it is a fact that heaps of undifferentiated cells are found deposited in the characteristic growths (ganglioneuroma or chromaffin tumor). In a few of these tumors mesodermal as well as ectodermal tissue have been placed side by side (as myeloid, adipose and muscular tissue).

Transitional forms are also found. The malignancy seems to decrease in proportion to the advanced stage of differentiation and the increasing age of the host, while on the other hand, the differentiation of the embryonic tissue into ganglioneuroma and chromaffin tumors increases in ratio to the age of the individual.

We shall first discuss the malignant neuroblastomas of which this paper mainly treats. Attention had for a long time been called to the fact that malignant tumors now and then occurred in the adrenals and the liver of newly born infants and quite young children. These neoplasms, in which were found large necrotic areas and hemorrhages, were mostly regarded as lymphosarcoma and round-cell sarcoma and described as such, especially by English and American authors in the eighties and nineties. In the Norwegian literature two cases are described by F. G. Gade, one of which, according to the description in all main features, corresponded with neuroblastoma.

Little by little it became evident that these growths had certain structural peculiarities in common with the nervous system. Such stress was laid on the similarity of the tumor structure with glia tissue that they were named glioma (Ribbert and his pupil Kuster). However, comparatively early, a deeper understanding of these growths was shown in the works of Marchand (1891), who maintained that the tumors were made up of embryonic undifferentiated cells of the sympathetic system (which was also pointed out by Kretz and particularly by Wiesel).

But the generally accepted view, which later was recognized as correct, that these tumors arise from embryonic, sympathetic nerve cells, neurocytes, directly, was first conclusively proved by James H. Wright⁵ in 1910. He introduced the name neurocytoma or neuroblastoma. Later followed a number of papers on similar tumors, among which may be mentioned the more exhaustive ones by Pick and

3 Landau *Frankl's Ztschr f Path*, 1912, xi

4 Wahl *Jour Med Research*, 1914, xxv

5 Wright, James H. *Jour Exper Med*, 1910, xii

Bielschowsky (1912)⁶, Landau (1912) and Herxheimer⁷ (1913), Wahl (1914)

The peculiar structure of these tumors as first minutely described by J H Wright is as follows The growths are made up of numerous, closely packed, small, atypical cells with strongly colored round or oblong nuclei, a scanty protoplasm, and with partly faint processes, often forming a kind of syncytium, appearing like the embryonic, undifferentiated cells of the sympathetic system Between the cells is a more or less distinct, finely fibrillated network, which has been definitely proved to be nerve fibers No ganglion cells are present The cells are often arranged in characteristic rosette form, with a pale colorless center composed of numerous fibrillae, surrounded by radiating, cylindrical cells, as in the structure of certain gliomas of the retina and the central nervous system

Then again the cells are arranged in larger heaps and the fibrillae are separated by strands of connective tissue or in bundles which taper into colorless fibrillar strands At times no differentiation is found These fibrillae are not glia fibers nor connective-tissue fibers, but in all probability are embryonic nerve fibers The structure greatly resembles a round-cell sarcoma, a glioma, a lymphosarcoma or an alveolar sarcoma The tumors are congenital They are only found in the newborn, in infants or in children, who have died during the first years of their existence About thirty cases have been described up to the present, all in children, of which twelve were not above 3 months of age, eighteen not above 1 year, and only eight in twenty-six being more than 1 year old The oldest child in whom such a tumor was demonstrated was 9 years old The growths occurred twice as often in girls as in boys Whether this is just a coincidence, cannot be determined now The site of the tumors was most frequently in the adrenals, in a few cases in the sympathetic nerve and once in the coccygeal gland As a rule they are single, at times multiple, the disease is hardly systemic They are exquisitely malignant Their growth is infiltrating and progressively destructive, they have a tendency to cause necrosis and hemorrhages and to form metastases, through the lymphatics to the lymph glands as well as through the blood vessels preferably to the liver, in which may be found scattered nodes or a diffuse infiltration, and sometimes but seldom to the osseous system, and then, especially to the cranium or to other internal organs The structure of the metastases is often so atypical that only a diagnosis of sarcoma can be made

⁶ Pick and Bielschowsky Ztschr f d Gesellsch f Neurol u Psychiat, 1911, vi

⁷ Landau and Herxheimer Beitr z path Anat u z allg Path, 1913, lvii

In order to throw some light on these growths I shall briefly relate some of my own observations during recent years

CASE 1—June 7, 1913, I received from Dr Justus Barth a tumor which he had just removed from a 3-year-old child. It was situated anteriorly on the sacrum and was very difficult to remove as it had infiltrated the surrounding tissues and also the large pelvic veins. One of these became perforated so that it had to be sutured. As a consequence of pulling on the tumor, the child's pulse became very feeble—the tumor seemed to be closely connected with the sympathetic nerve. The child, who had lost considerable blood, died on the table. No signs of metastasis were present, a post-mortem examination, however, was not made. The tumor was orange-sized, somewhat oblong, of a very soft consistency. It was surrounded by a connective-tissue capsule, which was penetrated in several places, especially in a larger (5 by 7 cm) area, where the substance was greatly broken down, quite mushy and soft, color, yellow or yellowish-red. On section the surface showed partly a more grayish,



Fig 1—Section of neuroblastoma. Numerous rosettes and tubes surrounded by neuro-epithelium.

partly a more yellowish color, particularly in those places where extensive necrotic changes had taken place. Those areas were intensely yellow in color. Hemorrhagic foci were not seen. It was found that the tumor was subdivided into smaller and larger nodules or spaces in which were deposited quite soft, grayish-white tumor masses. On the surface, corresponding to the nodules, were many small protuberances.

Microscopic Examination—On first sight the structure reminded one of an epithelial tumor, but on closer examination it proved to be an embryonic not yet differentiated nerve tissue. The major part of the growth was necrotic to such an extent that its structure only could be recognized in small sections. It was made up of numerous small cells with highly colored nuclei and very sparse protoplasm. The cells were closely packed and separated by a faint fibrillar network. The cells were atypical, from them alone no conclusion could be drawn as to their nature, but their mode of arrangement brought

out their peculiarities. They were arranged in larger, well-defined groups surrounded by heavy connective-tissue walls.

The structure presented a varying view. Most often the cells were arranged in long, tortuous bands, the cells close together, side by side in one or more layers (Fig 1). When several bands ran parallel to one another, long, adenoma-like formations were produced. Their periphery was formed by cylindrical epithelium-like cells. The centers were filled with fine, fibrous or granular masses, organically connected with the peripheral cells. The whole "tube" was separated from similar tubes by a sparse, vessel-carrying, connective tissue framework.

Where the "tube" was cut across, rosette-like formations were seen, that is, a layer of strongly colored small cells around a fine-fibred granular mass in the center. Rosettes formed by closely packed cylindrical cells around a small vessel were observed also (Fig 2). The tumor was principally made up of these cellular structures, but in close organic connection were seen other areas,



Fig 2—Neuroblastoma. Undifferentiated nervous tissue in large masses with rosettes. Above numerous rosettes and tubes.

poorer in cells, paler and more decidedly fibrillar. Here the cells were more fusiform, had small, oblong nuclei and almost no demonstrable protoplasm, but were surrounded by a fibrous substance, which often arranged itself into long bundles. Large heaps of cellulofibrillary areas again formed sharply defined accumulations of tumor tissue well separated from the surrounding connective-tissue stroma (Fig 3). Finally were seen large heaps of the very small cells with round nuclei and very sparse protoplasm in an almost confluent arrangement, forming a kind of syncytium or multinuclear conglomeration, that is, the cells were packed more closely together, but without being differentiated into rosettes. These parts of the tumor gave the impression of representing a still more undeveloped stage of the growth.

CASE 2—Another case of neuroblastoma, a primary cystic tumor of the adrenal with liver metastasis, occurred in a 6½ year old child. As the case gave the same microscopic picture as the former, it will be presented only in

its main features. The child was sick for about one month with signs of a rapidly growing tumor of the liver. Post-mortem examination revealed a considerable enlargement of this organ which was studded with soft, grayish-red, large, partly hemorrhagic nodules. The left adrenal was converted into a fluctuating "cystic" mass, as large as a goose egg, containing a bloody fluid mixed with tumor particles. Microscopic examination showed in the wall of the cyst a tissue consisting of atypical, quite undifferentiated cells which, as to shape and arrangement, entirely corresponded with those found in the first case.

In the older Norwegian medical literature are two cases of primary adrenal tumors described by F. G. Gade. These had their starting point in the adrenals of children 4 and 6 years old. They were described as and were supposed to be round-cell sarcomas. It must be assumed, however, in the light of our present knowledge, that they were malignant neuroblastomas.

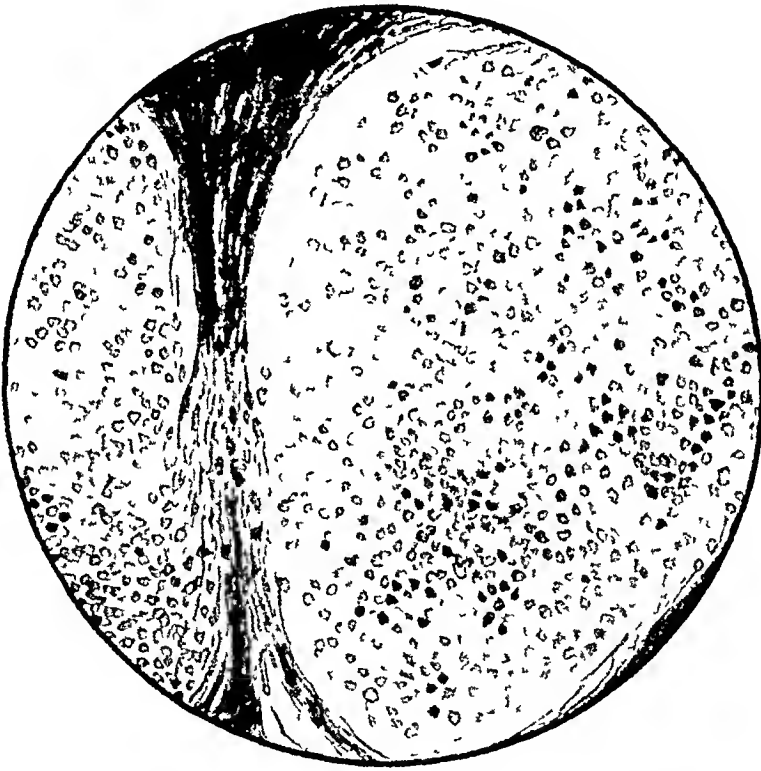


Fig. 3—Numerous clumps of cellular nervous tissues

In connection with the two cases of genuine, malignant neuroblastomas must be briefly mentioned a case of teratoma in which proliferation of nerve tissue was the most characteristic feature and which developed into tumors that structurally gave all evidence of being neuroblastomas. It is not uncommon that teratomas in the most different locations as, for instance, in dermoid cysts of the ovary, contain comparatively large masses of nerve substance in a lively process of development. Such great masses as in Case 3, however, are seldom encountered and add to its particular interest, as almost the entire tumor was a neuroblastoma. Judging from the great masses of

nerve tissue which make up this and similar tumors, it seems rational to suggest that possibly some malignant neuroblastomas originally have been teratomas in which the nerve elements mainly proliferated and finally took the lead. The existence, repeatedly proved, of other tissues in such tumors might also speak for this assumption.



Fig 4—Tumor in sacral region

CASE 3—In the fall of 1905, Dr J Barth, assistant physician to the Maternity Hospital at Christiania, sent me a malformed fetus with a large tumor of the sacral region. The fetus was 17 cm long, almost normally developed and about 4 months old. From the gluteal region reaching from the penis and scrotum toward the loins proceeded a pyriform growth measuring in length $7\frac{1}{4}$ cm, in width $6\frac{1}{2}$ cm, and in thickness $3\frac{1}{2}$ cm. Its greatest circumference was 15 cm (Fig 4). The somewhat narrower part connecting it with the body of the fetus measured 9 cm. Fetus and tumor weighed 250

grams Except at its inferior pole the neoplasm was covered with integument The surface was even and smooth The consistency somewhat uneven, mostly soft The integument was not everywhere firmly attached On its entire anterior aspect it formed only a membrane loosely connected with the inside Posteriorly it could be separated from the underlying tissue only at its inferior extremity After cutting through and lifting up this membrane anteriorly the following picture was revealed

Three oblong rounded bodies were separated by relatively deep furrows which, however, posteriorly were united by a common substratum Between the two first eminences ran a band 2 cm wide which gradually merged into the substance of the third On section these three tumors had a nearly similar appearance They were covered with a thin, smooth membrane, and consisted of a soft grayish to yellowish almost necrotic tissue which broke into fragments on being cut On opening the central canal of the sacrum it was found closed posteriorly A communication reaching about into the center of the tumor seemed to be maintained below This, however, could not be definitely decided on account of the softened condition of the tissues



Fig 5—Large masses of atypical, undifferentiated nervous tissue with indication of a large rosette

Microscopic Examination—The various sections of the tumor contained the same kind of tissue large accumulations of small round cells with large nuclei and sparse protoplasm subdivided by connective-tissue strings The exceedingly numerous cells were mostly in large heaps with no characteristic arrangement They were closely packed almost without intercellular substance (Fig 5) Only here and there where they were less numerous was seen an indistinct granular or fibrillar intercellular substance which was colored yellow with Van Gieson's stain In other places the cells were arranged in a more characteristic manner, forming large wavy bands, the cells being placed in rows of 6, 8 or 10, otherwise in the same atypical way as elsewhere The tissue around the cells was devoid of nuclei and consisted only of a finely granular, or in places of an indistinct fibrillar, intercellular substance Finally places were observed where the cells had arranged themselves in rosettes around an

oval or circular space filled with heterogeneous granular or fibrillar tissue (Fig 6) In other words the tumor mass consisted of embryonic, proliferating, not yet differentiated nerve substance The arrangement reminded one somewhat of an ependyma around the central canal The tumors also contained a few lumps, which supposedly were embryonic cartilage

The microscopic structure corresponded in every detail with the structure of neuroblastoma, and the tumor should be classified as such The presence of some embryonic cartilage has no contrary bearing

The most recently described group of tumors coming under this head is the paraganglioma or chromaffin tumor This has as yet only been demonstrated in a comparatively small number, about 12 or 15 up to the present, mostly since 1909 The frequency has increased greatly during the last year since they have received more attention



Fig 6—Nervous tissue, slightly differentiated, with several rosettes

The paraganglioma may develop from any of the paraganglia of the sympathetic nerve, but most frequently from the medulla of the adrenals (“struma suprarenalis medullaris”) and the carotid gland A single case has been observed in the region of the coccygeal gland, supposedly originating from it These growths are sharply limited, mostly solitary, occurring as a rule in more advanced age, with about equal frequency in men and women They are often casually detected at postmortem examinations They should be considered as typically benign tumors with a characteristic structure, made up of large epithelial-like cells arranged in heaps, separated by a very sparse, vessel-carrying stroma “peritheliomas” (as in organs with an internal secretion) The cells are chromaffin and contain adrenalin, a fact

which may be readily demonstrated by the fixation fluid in which it dissolves. This is, however, not always the case, because the cells may be in a transitional, not fully developed stage, and hence may not yet have acquired the chromaffin property. These tumors should be considered as epithelial growths on the borderline between typical and atypical neoplasms. Of great interest is the fact that some of them appear more as diffuse hyperplasias, especially in the adrenals, and that they repeatedly have been found in individuals afflicted with multiple neurofibromatosis as, for instance, in the sympathetic nerve.

The most important reports on tumors of the adrenal medulla are the following:

Manasse (1896) A tumor the size of a hen's egg in the medulla of the adrenal in a man aged 70.

Stange (1902) A round tumor, size of an apple, of chromaffin tissue in the sympathetic nerve of Zuckerkandl's organ. The tumor consisted of polymorphous cells and giant cells, which were colored yellowish-brown with chrome salts.

Suzuki⁸ Three cases in the adrenals, (1) a 10 cm large, round tumor in the adrenal of a man aged 62, (2) a tumor 0.5 cm large in a woman aged 60 with multiple neurofibromatosis, and (3) a similar tumor in a woman aged 82.

Wiesel and Neusser A tumor in the adrenal of a man aged 43. The tumor was cystic and hemorrhagic and made up of chromaffin and other cells of the sympathetic nerve.

Hedinger⁹ in 1911 described a "struma medulla cystica suprarenalis," an 11 cm round tumor in a 37-year-old woman. The tumor contained large polymorphous epithelium-like cells with alveolar arrangement separated by narrow connective-tissue septa, abundantly supplied with blood vessels, also large giant-cell-like formations without adipose tissue but partly with glycogen. Some gave the typical brown color with chrome. It contained also possibly some ganglion cells, besides bundles of nerve fibers. The structure reminded one considerably of hypernephroma.

Herde¹⁰ Two cases, (1) a 6 or 7 cm sized tumor, hemorrhagic and cystic, with chromaffin cells, in a 62-year-old woman, (2) bilateral suprarenal tumors in a 45-year-old woman (1 and 3 cm in diameter, respectively). These growths were made up of chromaffin cells and giant cells.

Wegelin¹¹ A 5 cm sized tumor with chromaffin cells and adrenalin in the solution (brown color) in a 39-year-old woman. The cells were quite polymorphous.

⁸ Suzuki Berl klin Wchnschr, 1909, 1910

⁹ Hedinger Frankl Ztschr f Path, 1911, vii

¹⁰ Herde Arch f klin Chir, xcvi

¹¹ Wegelin Verhandl d Path Gesellsch, 1912

Kowashima¹² found in a case of multiple neurofibromatosis a diffuse hyperplasia of the adrenal medulla. He thinks that both diseases are the same, namely a congenital anomaly which may affect the cerebrospinal, the sympathetic and the peripheral nerves and the adrenal medulla with its chromaffin cells.

Herxheimer¹³ found in a 55-year-old man afflicted with neurofibromatosis, a tumor in the suprarenal capsule as large as a hazelnut. Some similar growths in the carotid gland should be mentioned, namely, a case described by Marchand, 1891, by Oberndorffer,¹⁴ and by Monckeberg.¹⁵ The last was a tumor in the carotid gland of a 52-year-old man. Beitzke describes "strumia intercarotica." It was a plum-sized brownish-red tumor of characteristic structure in an old woman of 56. The tumor varied in appearance in periphery and center. In places were large nuclei, rich in chromatin.

The benign tumors of the carotid gland are as a rule found in grown people from 16 to 74 years of age. Most of them have been surgically removed. They were intimately connected with the carotids, brownish-red to grayish-brown in color, of varying consistency, well supplied with vessels, alveolar in structure and more or less similar in character to the structure of the carotid gland.

To these cases of tumors in the adrenal medulla may be added a case of multiple tumors, some of which may be supposed to have started in the adrenal medulla.

CASE 4—Multiple tumors. (1) Hypernephroma in a kidney, (2) cystadenoma in the pancreas, (3) chromaffin tumor in the region of the suprarenal capsule and (4) a similar tumor in the region of the kidney. This patient, a man aged 47, died from a large abdominal neoplasm of the left renal region. It had given symptoms for about one year. At the post-mortem examination the following conditions were found:

(1) The left kidney had been converted into a large tumor reaching from the superior spine of the ileum to the diaphragm. It was retroperitoneally situated. Its surface was studded with large nodules and it was very soft. Remnants of renal tissue were seen in places as a thin covering of the tumor. It consisted to a great extent of large, yellowish-white, necrotic material which in places was broken down forming a soft, reddish-gray, almost pus-like mass. In the periphery were less necrotic, reddish-gray tumor nodules. The renal veins were filled with the same grayish-white tumor masses extending into the inferior vena cava which was filled entirely with a cylindrical, yellowish-red tumor mass reaching clear into the right atrium of the heart. In the right kidney at its superior pole were soft reddish-gray tumor nodules—metastases from the tumor of the left kidney. Numerous metastatic deposits of the same nature were also found in the lungs and liver.

Microscopic Examination—In the principal tumor of the left kidney and in the metastatic growths it concerned the same structure, namely hyper-

12 Kowashima Virchow's Archiv f path Anat, 1911, cciii

13 Herxheimer Beitr z path Anat u z allg Path, 1913, lvii

14 Oberndorffer Centralbl f allg Path u Path Anat, 1905, xvi

15 Monckeberg Beitr z path Anat u g Allg Path, 1905, xxviii

nephroma The stroma was a sparse, connective-tissue reticulum with vessels, the long, solid alveoli were filled with large clear epithelial cells with oval, distinct nuclei and a clear colorless protoplasm The same regular structure was found throughout, corresponding with the usual picture of a hypernephroma and had structurally no similarity to the "brown tumor"

(2) In the tail of the pancreas was a conglomeration of cysts One of these was as large as a walnut and was filled with a clear yellow fluid In its walls were trabeculae with prominent edges and in the walls of the large cysts could be seen the outlines of smaller ones

Microscopic Examination—This revealed scattered larger and smaller cysts, which were lined with a single layer of flattened epithelium, in places detached into long ribbons The walls around and between the cysts consisted of a hyalin connective tissue with small deposits of pigment and poor in cells The parts of the pancreas in close proximity to the tumor, showed normal conditions No transitional stage between the tumor and the pancreas can be demonstrated Diagnosis Cystadenoma of the pancreas



Fig 7—Irregular distribution of adrenal substance in boundary between tumor and adrenal

(3) To the inner side of the upper pole of the right kidney and loosely connected with it by connective tissue was a round tumor 6 or 7 cm in diameter sharply limited and covered with a hard calcareous capsule Inside of this was a soft mass grayish-red or grayish-brown in the periphery and gray-white in the center, somewhat spongy and cystic

The tumor showed on section a great many thick-walled vessels containing blood and lined with a regular layer of endothelium The walls of the vessels were in many places greatly swollen and hyaline In the softer parts was a hyaline connective tissue, poor in cells, with long narrow bands of proliferating, angular, polymorphous cells with large nuclei, resembling endothelial or epithelial cells Everywhere was an abundance of vessels with marked hyaline degeneration In the periphery of the tumor were epithelium-like cells arranged in small heaps, irregular in shape with large nuclei, rich in chromatin Diagnosis hemangioma Brown tumor from adrenal tissue (?)

(4) Above the right kidney, loosely connected with the tumor just described, and to the right kidney was a sharply defined, soft, grayish or brown tumor, resembling somewhat liver tissue. It consisted of two parts, the larger the size of a large walnut, the smaller larger than a hazelnut, united by a fibrous capsule. On section was seen a homogeneous, spongy surface with some larger and smaller spaces. On the upper surface were parts of the right adrenal, especially of its cortical portion. The growth was situated between the right kidney and the adrenal. It was, however, entirely separated from the kidney by fibrous tissue, but was intimately connected with the adrenal, which gradually merged into the tumor, especially at the hilus, at a point where the two nodules joined, adrenal tissue abundantly supplied with vessels penetrated into the neoplasms.

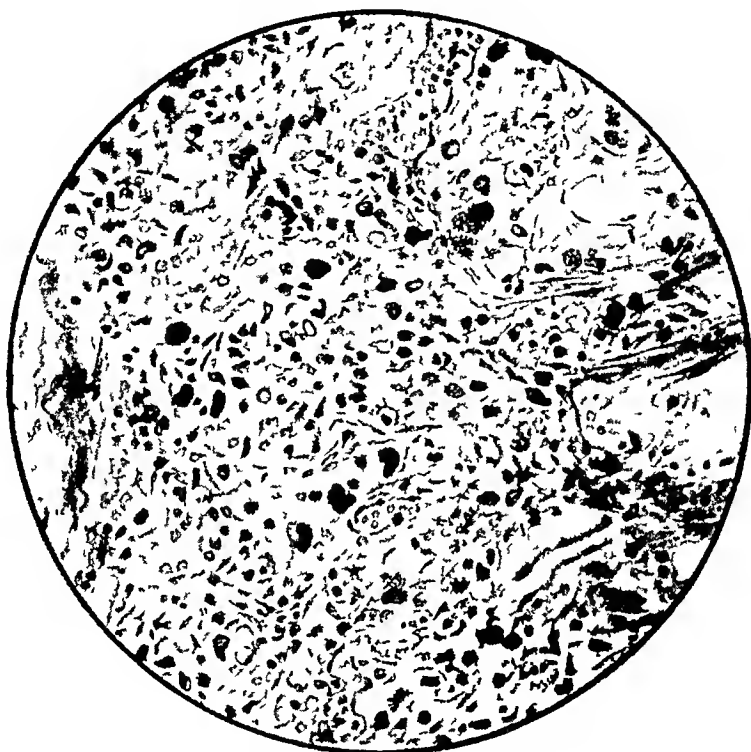


Fig 8—Large, irregular, more or less polyhedral cells forming parenchyma of tumor

Microscopic Examination—At the point of junction with the adrenal was an irregular distribution of suprarenal tissue in a heavy fibrous band forming the boundary between the tumor and the adrenal. Distributed in the fibrous tissue were islands of epithelium of the same kind as in the cortical portion of the adrenals. Such islands were also scattered along the fibrous borderline, in a few places on the surface of the tumor, but particularly in a narrow strip of fibrous tissue which continued into the tumor (Fig 7).

The medullary portion was somewhat irregularly arranged in certain parts. Scattered heaps of somewhat atypical epithelium occurred in a spongy (lymph-angiomatous?) tissue with several nerves. The tumor was very rich in cells of many shapes, but otherwise homogeneous in its structure. The abundant supply of vessels and nerves was striking. It contained a multitude of blood vessels, many with very thin walls. Others had swollen walls with hyaline degeneration and few cells. In other places was a fine fibrillar network with narrow slits—edematous. There were also numerous large and small blood and lymph vessels and larger spaces (sinuses) lined with endothelium, giving the structure a great resemblance to a hemangioma or lymphangioma. It was also traversed by numerous large branching nerves whose twigs were

ultimately lost between the tumor cells. In many places was an amorphous, yellowish pigment, apparently remnants from hemorrhages.

The tumor parenchyma was made up of large, irregularly shaped, angular, polyhedral, sometimes round, more or less epithelial-like cells. The nuclei were also irregular in shape, partly large and swollen and partly multinuclear. They were arranged side by side in small heaps or bands without discernible intercellular substance, but with a fine connective-tissue network separating the heaps. The similarity to the medulla of the adrenals was quite noticeable in places. Many cells had a faint brownish pigmentation. Some had a good deal of granular protoplasm, others had very large nuclei with abundant chromatin, a few had multiple nuclei. Beside these epithelial cells were numerous smaller connective-tissue-like cells arranged partly as a connective-tissue stroma among the tumor tissue. Finally were observed, scattered small atypical round lymphocyte-like cells, although nowhere could a genuine inflammatory infiltration be demonstrated. Ganglion cells or cells similar to these were not found. In specimens fixed with chrome solution were some few large polyhedral cells with diffusely brown colored protoplasm. It is to be regretted that the post mortem was not made before about twenty-four hours after death. The alcohol in which the tumor later was preserved did not turn brown or give the reaction for adrenalin.

This case is very interesting in many respects. First on account of the multiple neoplasms of—at least apparently—entirely different kinds of growths in various organs, in the pancreas, the adrenals, and free in the abdominal cavity. The polymorphous nature of the tumors, however, may not have been so great because the tumors were principally epithelial—a cystadenoma in the pancreas, a large atypical hypernephroma in one kidney with metastatic deposits, arising from the epithelium of the adrenal corticalis—further an adenomatous or “strumous” growth arising from the medullary portion of the other adrenal. But to these was added the evidently very old abdominal tumor well surrounded by a calcareous capsule. This tumor on microscopic examination gave the impression of being a hemangioma arrested in its growth. On renewed and closer investigation, however, it was found that more importance should be attached to the remnants of the original tumor or parenchyma disclosed in the grayish-brown strip along the periphery of the growth, which was made up of small heaps of polymorphous, epithelial-like cells, practically identical with the cells of the struma of the right adrenal. When the intimate connection with the “brown tumor” of the adrenal is considered, the evidence goes in favor of assuming, that both had the same origin, with the reservation, however, that the encapsulated tumor, which now consisted mainly of blood vessels or more correctly speaking remnants of such, was a further step in the development of the brown tumor, that is, it had been arrested in its growth. The tumor parenchyma was mostly degenerated and the blood vessels hyaline. This is most likely the correct interpretation, and if so, this tumor must also be classified with the epithelial growths. Very interesting were the scattered

islands of adrenal tissue found in the capsule, which surrounded the brown tumor and also in the adjacent parts of the right adrenal. These represented principally the cortical portion. It was further of the greatest interest that these *veinite keime* were found in the right adrenal coincidentally with an atypical hypernephroma of the other side. To assume that a similar abnormality might be the starting point on the left side seems reasonable. Great stress should be laid on the intimate connection between the "brown tumor" and the right adrenal as well as on the existence of isolated islands of adrenal medulla and supposed growth or development of the brown tumors from the medulla of the adrenals.

The microscopic conditions, the gradual transitions and the brown color point decidedly in favor of this theory. Still more conclusively does the microscopic picture strengthen the evidence—the description which so far as conclusions can be drawn from a fixed specimen shows that the tumor cells and the entire tissue correspond in structure and appearance with that of the adrenal medulla in the most normally constructed parts, while they deviate more and more therefrom in the more cellular, atypical sections.

Important points in the diagnosis of chromaffin tumor are the great abundance of vessels in places and the rich vascular supply of the stroma (see the hemangioma-like structure of the tumor next to the abber from which the capsule has been removed), next the existence of nerves, although nonmedullated, in the tumor—a frequent occurrence—which, however, also speaks in favor of adrenal origin, further, the similarity to other tumors of the same type (Hedinger's case), and finally the brown color of the tumor itself and the fact that some, although only a few, of the large epithelial-like cells took on a brown color after having been treated with the chrome solution. The post-mortem examination was unfortunately made so late that the chances of obtaining chrome fixation were slight, so that the characteristic color was obtained only in a few places. Another diagnostic point would have been the chemical demonstration of adrenalin in the extract from the tumor (as in aqueous extracts obtained from normal, adrenalin tissue), but the attempts in this direction had a negative result¹⁶. Everything taken into consideration, it seems certain that

16 An extract is made from quite fresh adrenal tissue in physiologic salt solution. After standing for about eighteen hours, adrenalin can be demonstrated in the extract by the following procedures: (1) By treatment with a dilute solution of ferric chlorid— Fe_2Cl_6 —a greenish-yellow color turning into reddish is obtained (Vulpian's reaction), (2) with dilute tincture of iodine a reddish color is obtained, (3) with a dilute 0.1 per cent potassium sulphate solution a red color is obtained, (4) with a 2 per cent muric chlorid solution and heating, a red color develops (Camesatti's reaction).

this adrenalin tumor (and also very likely the other hemangioma-like) originated in the medullary substance of the adrenals, being to a great extent chromaffin. In other words the tumor should be classified as a paraganglioma, possessing as it does the typical qualities of these neoplasms—a classification which also is corroborated by a former accidental find at the postmortem of an elderly man. One of the tumors was even arrested in its growth, had been encapsulated and had to a great extent undergone degenerative changes.

POTASSIUM POISONING IN NEPHRITIS [†]

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Functional studies of the kidney have afforded many striking possibilities and many interesting problems. The subject is so new, the methods so exact, and the interpretation of results so little understood, that the subject is an ideal one for research.

During the past year, I¹ had an opportunity to study with Dr Frothingham the different nitrogenous diets in chronic nephritis from a functional point of view. In these cases, we found, as has been demonstrated by Widal² and others, that certain types of chronic nephritis were unable to excrete salt normally. In many cases, 10 gm of sodium chlorid, when added to the diet, was excreted poorly, or not at all.

Bunge,³ several years ago, in observations on animals and normal individuals, found that the increased intake of potassium salts caused an increased sodium salt excretion, and vice versa. This observation suggested to us the possibility of causing an increased sodium salt excretion, by the addition of potassium salt to the diet, in cases of nephritis in which it had been proved that there was a decreased ability of the kidney to excrete salt.

Selected cases with chronic nephritis were studied in the wards of the hospital. The methods used and the data recorded are exactly the same as those used in the paper¹ previously referred to. In this problem, each case was first studied functionally, and classified. In certain cases, when it had been proved that there was definite inability of the kidney to excrete 10 gm of added sodium chlorid, the patient was given potassium chlorid. The salt was administered in a single dose of 5 or 10 gm, in 150 c c of water at 10 a m.

In some of the cases there was an apparent increase of the salt excretion following the increased potassium chlorid intake, in other cases no apparent effect was produced.

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1 Frothingham, C, and Smillie, W G. A Study of Different Nitrogenous Diets in Chronic Nephritis, *THE ARCHIVES INT MED*, 1915, xv, 204.

2 Widal. *Mouvement Med*, 1913, i, 1.

3 Bunge. *Ztschr f Biol*, 1873, ix, 104.

Four typical tables will be given

CASE 1 (1170) —This was classified clinically as of chronic nephritis, arteriosclerosis and hypertension Functionally, there was moderate inability to excrete salt, with practically normal nitrogen excretion On the 17th, 5 gm of potassium chlorid were given No increase of salt excretion occurred No ill effects were produced Results are given in Table 1

TABLE 1—RESULTS OF TEST IN CASE 1 (1170)

Date	Fluid Intake c c	Urine		Nitrogen		Chlorid		Mg N per 100 c c Blood	Per Cent Phthal ein in 2 Hrs	Blood Pressure
		24° Am c c	Sp Gr	Intake Gm	Output Gm	Intake Gm	Output Gm			
May 9		1,880	1 016	11 2	12 6	4 0	14 0	34 2	50	230-130
May 10		745	1 022	11 2	10 6	4 0	3 2			
May 11		890	1 021	11 2	12 4	4 0	3 4			
May 12		1,515	1 020	11 2	12 2	4 0 NaCl 10 gm	9 5			
May 13		1,530	1 014	11 2 Urea 20 gm	12 2	4 0	5 1			
May 14		1,530	1 015	21 2	16 4	4 0	3 0			
May 15		1,160	1 017	11 2	12 8	4 0	1 5			
May 16		1,340	1 017	11 2	14 7	4 0	3 6		59	
May 17	700	1,060	1 016	11 2	10 6	4 0 KCl 5 9 0	3 5	28 5		
May 18	1,310	840	1 020	11 2	10 3	4 0	2 8			
May 19	1,480	980	1 020	11 2	11 5	4 0	2 8			

CASE 2 (1072) —This was classified clinically as of chronic nephritis with hypertension Functionally there was marked inability to excrete salt, and moderate inability to excrete nitrogen On May 5, 5 gm of potassium chlorid were given, which was followed by an immediate increase in the chlorid output No ill effects were produced Results are given in Table 2

TABLE 2—RESULTS OF TEST IN CASE 2 (1072)

Date	Fluid Intake c c	Urine		Nitrogen		Chlorid		Mg N per 100 c c Blood	Per Cent Phthal ein	Blood Pressure
		24° Am c c	Sp Gr	Intake Gm	Output Gm	Intake Gm	Output Gm			
April 16	1,100	1,480	1 015	10 7	3 1	4 0	7 2			190 100
April 17	1,300	1,100	1 010	9 7	3 0	3 0 NaCl 10 gm	1 2	31 8	60	
April 18	950	840	1 015	10 7	6 3	14 0	4 0			200 110
April 19	1,300	1,180	1 009	8 8 Urea 20 gm	3 5	3 0	2 7			
April 20	1,300	2,400	1 010	18 7	8 2	4 0	6 7			210 112
April 21	1,500	1,810	1 010	10 7	8 0	4 0	3 2			
May 3	1,350	1,460	1 003	4 0	4 8	4 0	1 5			170 98
May 4	1,200	1,090	1 010	4 0	4 6	4 0	1 9			
May 5	1,100	1,355	1 010	4 0	2 8	4 0 KCl 5 9 0	7 2	28 7	51	

CASE 3 (1154)—This was classified clinically as of chronic nephritis, with albuminuric retinitis and hypertension. Functionally there was a marked inability to excrete added sodium chlorid, with slight inability to excrete added urea. On May 17, 10 gm of potassium chlorid were added to the diet. No increase of salt excretion occurred. No ill effects were produced. Results are shown in Table 3.

CASE 4 (1097)—This was classified clinically as of chronic nephritis with hypertension. Functionally there was a moderate inability to excrete added sodium chlorid, and slight inability to excrete added urea. Ten grams of potassium chlorid were administered on May 8. This was followed by a definite increase in the salt excretion. No ill effects were noted. Results are shown in Table 4.

In two of the cases, additional potassium chlorid produced no increase of chlorid excretion, in two cases there was a definite increase of chlorid excretion. In none of these cases were there any ill effects from the potassium chlorid.

The next case reported was similar both clinically and functionally to those already given.

CASE 5 (1158)—A Russian Jewess, aged 42, married, entered the hospital May 5, 1914, complaining of headache and dizziness of a duration of two or three months.

Family History—The patient's husband and eleven children were living and well. She had had three miscarriages. There was no history of cancer, heart or kidney disease in the family.

Her habit has been to use a moderate amount of tea and coffee for years. Venereal disease is denied.

Past History—The patient had scarlet fever in childhood, otherwise her general health has been very good. There has been slight dyspnea on exertion for the past few years. Nocturia four or five times for several years has been a troublesome symptom.

Present Illness—Headaches have been frequent and severe for the past two or three months. Before this time headaches were rare. These headaches are now present two or three days of the week. There has been some dizziness for the past six weeks. A slight puffiness about the face and eyes was noted a month ago. About two weeks ago there was some nausea and vomiting.

Physical Examination—There is a definite hypertrophy of the heart, the left border being 13 cm to the left of the midsternum in the sixth space.

A blowing systolic murmur was present, best heard over the sternum. There is no edema of the face or extremities. The fundi of the eyes are normal. Blood pressure, systolic 245, diastolic 120. Physical examination otherwise is negative.

The urine showed a large trace of albumin, with granular casts and many white cells, but no blood. Phthalein test, two hours, 59 per cent, nonprotein nitrogen, 311 mg per 100 cc of blood.

Clinical Diagnosis—Chronic interstitial nephritis, hypertrophy of the heart, hypertension. Functional tests of the kidney, begun May 16, were not entirely satisfactory because of slight inability to control the urethral sphincter. The added sodium chlorid was poorly excreted, the added nitrogen was excreted fairly well. On May 24, 10 gm of potassium chlorid were given at 10 a m. Several hours after taking the salt the patient complained of weakness, abdominal distress and precordial pain. At 5 p m she was somewhat cyanotic, markedly prostrated, with regular, rather weak pulse, rate 80. There was considerable abdominal distress and vomiting during the night. At 6 a m on

TABLE 3—RESULTS OF TEST IN CASE 3 (1154)

Date	Fluid Intake c c	Urine		Nitrogen		Chlorid		Mg N per 100 c c Blood	Per Cent Phthal- ein	Blood Pres- sure
		24° Am c c	Sp Gr	Intake Gm	Output Gm	Intake Gm	Output Gm			
May 8	2,500	2,254	1 010	11 2	13 0	4 0	10 7	30 9	45	220 140
May 9	1,950	1,305	1 013	11 2	9 1	4 0	5 8			
May 10	1,350	1,020	1 021	11 2	10 3	4 0 NaCl 10 gm	5 3			
May 11	1,500	765	1 025	11 2	6 5	14 0	2 4			260 160
May 12	1,450	940	1 026	9 9	10 9	4 0	3 6			
May 13	1,800	600	1 016	11 2 Urea 20 gm	7 1	4 0	1 1			
May 14	2,700	3,300	1 010	20 7	19 1	4 0	4 3		60	230 150
May 15	2,100	940	1 020	9 9	9 3	4 0	1 4			220 150
May 16	1,900	1,830	1 017	9 7	9 3	4 0 KCl 10 gm	0 9			
May 17	2,100	1,150	1 011	8 7	7 3	14 0	2 7			
May 18	1,700	1,330	1 013	20 0	8 8	2 0	4 9			
May 19	1,650	1,245	1 013	22 5	12 0	4 0	2 8	35 1		

TABLE 4—RESULTS OF TEST IN CASE 4 (1097)

Date	Fluid Intake c c	Urine		Nitrogen		Chlorid		Mg N per 100 c c Blood	Per Cent Phthal- ein in 2 Hrs	Blood Pres- sure
		24° Am c c	Sp Gr	Intake Gm	Output Gm	Intake Gm	Output Gm			
April 30	1,200	1,030	1 019	6 1	8 5	6 0 NaCl 10 gm	4 0			195 110
May 1	1,500	890	1 022	6 0	7 7	16 0	4 5			
May 2	1,250	550+	1 018	6 0	3 5+	6 0	7 7+			
May 3	1,500	700	1 019	6 0 Urea 20 gm	4 7	6 0	5 5			180 100
May 4	1,200	1,465	1 017	6 0	12 5	6 0	9 6			
May 5	1,500	410+	1 020	6 0	2 6+	6 0	3 2+		51	
May 6	1,300	Lost	Lost	6 0	Lost	6 0	Lost			190 85
May 7	1,300	840	1 018	11 2	6 4	4 0 KCl 10 gm	5 2			
May 8	1,500	1,465	1 017	11 2	13 1	14 0	10 2	32 2		
May 9	1,500	980	1 020	11 2	7 0	4 0	5 8			200 100
May 10	1,200	1,165	1 022	11 2	13 4	4 0	5 2			
May 11	1,550	950	1 022	11 2	10 7	4 0	5 0		51	
May 12	1,250	1,310	1 013	11 2	8 0	4 0	3 7			

the 25th there was a sudden attack of intense cyanosis and marked prostration. There was a diminution in the amount of urine. There had been only a few blood cells in the urine but on the 26th a marked hemoglobinuria appeared. The nonprotein nitrogen in the blood had risen to 84 mg per 100 c c. The blood serum showed a definite hemoglobinemia. The spectroscope showed absence of methemoglobin.

TABLE 5—RESULTS OF TEST IN CASE 5 (1158)

Date	Fluid Intake c c	Urine		Nitrogen		Chlorid		Mg N per 100 c c Blood	Per Cent Phthal ein 24° 10'	Blood Pres- sure
		24° Am c c	Sp Gr	Intake Gm	Output Gm	Intake Gm	Output Gm			
May 16	1,495	960	1.016	6.0	6.4	16.0 NaCl 10 gm	2.2			
May 17	1,500	595	1.015	6.0	4.5	6.0	1.6			180/95
May 18	1,500	895		6.0		6.0				
May 19	1,675	400+	1.014	7.3 Urea 20 gm	2.6+	4.0	0.76+		52	
May 20	1,280	1,350	1.014	20.0	10.1	4.0	2.5			
May 21	1,330	1,385	1.012	7.0	8.0	3.5	2.3			170/85
May 22	1,310	440+		7.9		3.5				
May 23	590	1,460	1.011	6.3	8.9	3.5	2.2			
May 24	1,635	300+	1.016	5.4		KCl 10 gm	0.5			184/94
May 25	795	55+		0	?	0	?			
May 26	1,265	408	1.013	0.1	2.5	0	0.4	84.0		
May 27	1,400	310	1.012	0.0	1.9	0	0.3			
May 28	1,350	795	1.012	0.1	5.6	0	0.6			168/85
May 29	1,730	800	1.013	8.0	4.8	3.5	1.4			
May 30	1,760	775+	1.012	5.5	5.3	2.0	0.9			160/75
May 31	1,980	1,280	1.011	5.2	7.0	2.0	1.3			
June 1	1,630	1,200	1.011	8.1	7.2	3.5	1.7			
June 2	1,760	1,275	1.013	7.0	7.2	3.5	1.5			
June 3	1,650	1,700	1.011	8.1	10.9	3.5	1.8			
June 4	1,860	950	1.011	7.5	5.4	3.5	1.1			150/75
June 5	1,910	1,525	1.009	9.8	7.0	4.0	1.5			
June 6	1,810	1,205	1.009	10.5	5.6	4.0	1.2			
June 7	1,560	1,750	1.012	10.0	7.3	4.0	2.1	78.8		
June 20								66.2		
July 1								48.0		
July 4									32	120/58

There was a temperature of 100.8 on the 26th, with an increase in pulse-rate to 98. The temperature and pulse remained elevated for two days.

The symptoms were so severe and resembled so closely those of potassium chlorate poisoning, that at once the question arose as to whether a mistake had been made in the salt given. This was carefully checked and it was soon

proved that the salt given was potassium chlorid. This was substantiated by entire absence of methemoglobin formation. The patient slowly improved and returned to her former condition about June 10. Hemoglobinuria disappeared June 4 and blood cells were gone from the urine June 12. Nonprotein blood nitrogen on the 7th was 78.8 mg, falling to 48.0 on July 4. Throughout her stay in the hospital the blood pressure continued to fall, reaching 120-58 on discharge. She left the hospital with entire relief from headache and dizziness.

This case suggested to us that potassium chlorid in a dose which was harmless in normal individuals might be injurious in nephritis, and since the chlorin ion is devoid of action, that the poisoning must be due either to the action of the potassium ion, or to the "salt action." Since the "salt action" of sodium chlorid and potassium chlorid is the same, and since the patient did not react adversely to 10 gm sodium chlorid, it seemed probable that the poisoning was due to the potassium ion.

The chief action of potassium in experimental⁴ work, is a depression of the heart. There is at first, as a rule, an acceleration of the pulse, then the pulse becomes weaker and slower, and fall in the blood pressure occurs. Bunge⁵ has shown that some classes of people—Irish laborers and certain African tribes—have an intake of 50 gm potassium chlorid a day. The absence of effect on the heart is due to the rapid excretion of the salt by the kidney. Dr Reid Hunt, in an unpublished experiment, demonstrated that potassium salts in extraordinarily small amounts, produce death in guinea-pigs with the kidneys removed. The guinea-pigs when in normal condition, were injected with various potassium salts without ill effect, for the kidneys excreted the salt so rapidly that the concentration necessary to kill the animal was not reached. With the kidneys removed, much smaller doses of potassium killed the animal at once. Death was probably due to the action of the potassium ion on the heart. He calculated that a man who took a large portion of his food as potatoes, for example an Irish peasant, would have an intake of 10 times the fatal dose of potassium in a day. Were it not for the fact that potassium salts are so rapidly excreted by the kidneys, the effects might be very serious.

Experiments were now made in an attempt to correlate previous laboratory findings and our clinical experience with potassium poisoning in nephritis. Rabbits were given nephritis with uranium nitrate. The degree of nephritis was estimated by frequent blood nitrogen examinations. The same data were kept on rabbits as had been recorded in our patients, with the exception of the specific gravity of the urine, and blood pressure. The rabbits were given a large dose of

⁴ Macht Bull Johns Hopkins Hosp, 1914, xxv, 278
⁵ Bunge Arch f d ges Physiol, 1871, iv, 235

potassium chlorid by mouth while in a normal condition Uranium nitrate was then given subcutaneously to produce nephritis, and varying doses of potassium chlorid were added to the diet at different periods of the disease A few typical protocols will be given

Experiment 1, Rabbit 974—The animal was given 3 gm of potassium chlorid in 50 cc of water, with rapid excretion of the salt (4 gm in 50 cc of water sometimes caused death in the hot summer) A moderate nephritis was then produced by uranium nitrate The blood nitrogen rose gradually The animal was strong and showed no marked symptoms of illness On the 21st, when the nonprotein blood nitrogen reached 118 mg, one gm of potassium chlorid was given in 50 cc of water The animal died within fifteen minutes Necropsy showed typical lesions of acute uranium nephritis (Table 6)

TABLE 6—RESULTS OF TEST ON RABBIT 974, EXPERIMENT 1

Date	Fluid Intake c c	Urine c c	Nitrogen		Salt		Blood Nitro gen mg per 100 c c	Ura nium Nitrate Mg	Weight Gm	Remarks
			Intake Gm	Output Gm	Intake Gm	Output Gm				
Sept 16	210	150	0.7	1.4	0.15	0.13			1,800	
Sept 17	245	190	0.7	0.78	3.1	2.3	29.2			3 gm KCl
Sept 18	140	130	0.7	0.59	0.11	0.29	23.7	2		
Sept 19	200	100	0.7	0.43	0.15	0.12	25.8			
Sept 20	80	20	0.4	?	0.05	?	52.0			
Sept 21	50	Died			1.0		118.0		1,840	1 gm KCl

TABLE 7—RESULTS OF TEST ON RABBIT 958, EXPERIMENT 2

Date	Fluid Intake c c	Urine c c	Nitrogen		Salt		Blood Nitro gen mg per 100 c c	Ura nium Nitrate Mg	Weight Gm	Remarks
			Intake Gm	Output Gm	Intake Gm	Output Gm				
July 20	150	110	0.7	0.55	0.15	0.35				
July 21	200	210	0.7	0.32	3.15	1.50	22.9			3 gm KCl
July 22	200	180	0.7	0.56	0.15	0.52			1,850	
July 23	200	60	0.55	0.20	0.15	0.20		2		
July 24	190	154	0.55	0.48	0.15	0.11	38.2			
July 25	200	55	0.30	0.20	0.15	0.09				
July 26	30	48	0.14	0.25	0.04	0.07				
July 27	170	58	0.08	0.15	2.10	0.52	105.6			2 gm NaCl
July 28	140	68	0.40	0.17	0.10	0.39			1,800	
July 29	50	Died			1.0		140.0			1 gm KCl

Experiment 2, Rabbit 958—The rabbit was given 3 gm of potassium chlorid, with rapid excretion of the salt Nephritis was produced with uranium nitrate When the nonprotein blood nitrogen reached 100 mg, 2 gm of sodium chlorid

were added to the diet. No ill effects were produced, though there was poor excretion of the salt. Two days later 1 gm of potassium chlorid was given, with immediate death of the animal. There were no symptoms of weakness nor illness before the potassium chlorid was given. Necropsy showed characteristic lesions of acute nephritis. This experiment suggests that death is not due to "salt action," since the "salt action" of sodium and potassium chlorid is the same.

An attempt was next made to produce a moderate nephritis with repeated injection of uranium, adding to the daily diet small amounts of potassium chlorid.

TABLE 8—RESULTS OF TEST ON RABBIT 975, EXPERIMENT 3

Date	Fluid Intake c c	Urine c c	Nitrogen		Salt		Blood Nitro- gen mg per 100 c c	Ura- nium Nitrate Mg	Weight Gm	Remarks
			Intake Gm	Output Gm	Intake Gm	Output Gm				
Sept 16	20	75	0.7	1.1	0.15	0.08			2,040	
Sept 17	150	190	0.1	0.72	4.07	2.8	32.8			4 gm KCl
Sept 18	120	120	0.7	0.45	0.15	0.32	34.3	2		
Sept 19	50	38	0.1	0.59	0.02	0.05	33.9			
Sept 29								4		
Sept 30	50	155	0.65	0.56	0.62	0.45	28.4		1,920	0.5 gm KCl
Oct 1	50	130	0.55	0.48	0.62	0.49	36.7			0.5 gm KCl
Oct 2	50	105	0.40	0.80	0.63	0.51	53.2		1,860	0.5 gm KCl
Oct 3	50	150	0.55		0.65	0.69				0.5 gm KCl
Oct 4	50	85	0.55	0.27	0.65	0.48	60.8			0.5 gm KCl
Oct 5	50	150	0.70		0.63	0.70		6	1,770	0.5 gm KCl
Oct 6	50	150	0.35	0.70	0.60	0.64	53.2			0.5 gm KCl
Oct 7	50	120	0.3		0.60	0.56				0.5 gm KCl
Oct 8	50	100	0.55	0.57	0.58	0.45	68.4			0.5 gm KCl
Oct 9	50	60	0.50	0.14	0.60	0.38				0.5 gm KCl
Oct 10	50	140	0.60	0.49	0.55	0.82				0.5 gm KCl
Oct 11	50	140	0.60	0.48	0.60	0.63	54.6		1,760	0.5 gm KCl
Oct 12	50	180	0.55		1.13	1.20				1 gm KCl
Oct 13	50	240	0.12 Recov- ered		1.15	1.1	57.9			1 gm KCl

Experiment 3, Rabbit 975—Four gm of potassium chlorid were readily excreted on the 19th. Two mg of uranium nitrate gave no increase in non-protein blood nitrogen and the data are omitted. On the 29th four mg of uranium nitrate were given, with moderate gradual increase of blood nitrogen. Though the nonprotein blood nitrogen rose to 60 mg per 100 c c, potassium chlorid was readily excreted and no symptoms were evident. On October 5, 6 mg of uranium nitrate were given. The nonprotein blood nitrogen rose almost to 70 mg, but the potassium chlorid was well excreted and the animal recovered.

Experiment 4—This experiment is similar to Experiment 3. Moderate nephritis was produced by repeated injections of uranium nitrate, and potassium chlorid was given at various stages of the disease. The salt was well excreted until the nonprotein blood nitrogen became 100 mg. In this case as in the others, 1 gm. of the salt caused sudden death.

TABLE 9—RESULTS OF TEST ON RABBIT 978, EXPERIMENT 4

Date	Fluid Intake c c	Urine c c	Nitrogen		Salt		Blood Nitro- gen mg per 100 c c	Ura- nium Nitrate Mg	Weight Gm	Remarks
			Intake Gm	Output Gm	Intake Gm	Output Gm				
Sept 24	200	80	0.7	0.8	0.15	0.22			2,260	
Sept 25	310	280	0.68	1.0	4.1	3.4	23.8			4 gm KCl
Sept 26	240	180	0.7	0.87	0.15	0.26				
Sept 27	200	125	0.7	0.86	0.13	0.05	23.1	2		
Sept 28	245	170	0.7	0.88	0.13	0.12	26.5		2,260	
Sept 29	270	210	0.40	0.60	1.11	1.07	28.2			1 gm KCl
Sept 30	140	130	0.21	0.54	0.08	0.36	25.4		2,230	
Oct 1	125	130	0.30	0.47	0.07		36.4	3		
Oct 2	85	90	0.10	0.57	0.03	0.27	36.2		2,160	
Oct 3	120	100	0.50		0.07	0.17	68.0			
Oct 4	140	85	0.70	0.85	0.06	0.07				
Oct 5	170	110	0.50		1.1	0.47	57.2	5	2,100	1 gm KCl
Oct 6	80	75	0.10	0.42	0.03	0.30				
Oct 7	100	140	0.10		1.04	0.74	75.6			1 gm KCl
Oct 8	140	150	0.15	1.0	1.07	0.80				
Oct 9	180	68	0.10	0.38	0.10	0.14			2,040	
Oct 10	125	180	0.10	1.0	1.07	0.61	93.8			1 gm KCl
Oct 11	170	180	0.10	0.88	1.08	0.75				1 gm KCl
Oct 12	50				1.0		128.6			1 gm KCl
			Died							

Nine other experiments were carried out with similar results. The four examples given are typical. Frothingham, Fitz,⁶ and others who have worked with experimental uranium nephritis have shown that death does not occur in the rabbits until the nonprotein blood nitrogen has reached 150, 200, or even 250 mg. per 100 c c. Furthermore, the animals as a rule show definite symptoms of disease when death is impending.

For our experiments, as is shown, an attempt was made to produce a moderate nephritis, and to give the potassium chlorid before severe symptoms of the disease developed. In each instance, when the non-

⁶ Frothingham, C., Fitz, R., Folin, Otto, and Denis, W. The Relation Between Nonprotein Nitrogen Retention and Phenolsulphonephthalein Excretion in Experimental Uranium Nephritis, THE ARCHIVES INT. MED., 1913, XLII, 245.

protein blood nitrogen reached 100 mg per 100 c c the giving of 1 gm of potassium chlorid caused immediate death. The reason seems obvious, namely, the salt was absorbed by the gastro-intestinal tract, the kidneys were unable to excrete it, and, as in Hunt's experiments, a concentration was reached in the blood which was poisonous to the heart muscle.

Some of the conditions which were present in the experimental animals were also present in the patient, and it is reasonable to assume that some of her symptoms were due to the action of potassium on the heart muscle.

One symptom complex occurred in the patient which was not present in the experimental animals, namely, hemoglobinemia and hemoglobinuria, with rise in temperature and pulse. The cause of this phenomenon will be made the subject of a subsequent paper.

CONCLUSION

1 Rabbits with uranium nephritis of a degree sufficient to increase the nonprotein blood nitrogen to 100 mg per 100 c c, die with great suddenness following ingestions of 1 gm of potassium chlorid.

2 Their death is not due to "salt action," but is probably due to the action of the potassium ion on the heart muscle.

3 In human beings, potassium chlorid, in doses which have no effect on normal individuals, will cause acute poisoning in individuals with chronic nephritis.

4 This acute poisoning occurs because the salt, which is normally readily absorbed and very rapidly excreted, in nephritis is readily absorbed and not excreted, thus reaching a concentration in the blood which is injurious.

BOOK REVIEWS

ANOCI-ASSOCIATION By George W Crile, M D, Professor of Surgery, School of Medicine, Western Reserve University, Cleveland, and William E Lower, M D, Associate Professor of Genito-Urinary Surgery, School of Medicine, Western Reserve University, Cleveland Cloth, \$3 net Pp 259, with original illustrations Philadelphia and London W B Saunders Company, 1914

Under a strange and forbidding title is concealed a work that may seem out of place in the review pages of a periodical devoted to internal medicine. But internal medicine has many frontiers and on the borderline of surgery the internist should be as much at home as he is in his own special field. In this work are gathered the later results of a study of surgical shock by a facile surgeon and no less facile writer, a keen observer and untiring student who has had the advantage of thorough training in physiological methods and physiological principles. It is not intended to discuss here the facts or conclusions announced. Many details on which the kinetic theory of shock is based have yet to be confirmed. But the book is more than a new presentation of shock. It contains many surgical experiences and suggestions that will repay careful study by all. "The Treatment of Shock and its Prevention through Anoci-Association," by Dr Crile and Dr Lower, fills more than half the book and contains much of interest on many borderline subjects, such as abdominal operations, exophthalmic goiter, high and low blood pressure and postoperative morbidity and mortality. Other valuable chapters are included on "Nitrous Oxid Anesthesia," by Agatha Hodgins, "Anoci-Association in Its Relation to the Preoperative and Postoperative Care of Patients," by Samuel L Ledbetter, Jr. Numerous illustrations add to the value of the work.

DIETETICS OR FOOD IN HEALTH AND DISEASE By William Tibbles, LL D, M D, L R C P, M R C S, L S A Medical Officer of Health, Fellow of the Royal Institute of Public Health, etc. Octavo, 627 pages Cloth, \$4 00, net Lea & Febiger, Publishers, Philadelphia and New York, 1914

With the growing interest in metabolism and nutrition, as well as the desire for greater accuracy of feeding in health and disease, there is a demand for books containing the essential data. The present work finds some well-established competitors, yet it promises to make itself a field. It is well arranged, the various divisions are well balanced. The statements of facts and the discussions of unsettled questions are on the whole accurate and fair. On some points improvements might be made. Thus, the table of heat values of various foods gives the amounts in ounces, but as many diet kitchens are equipped with metric weights it would hasten the wider use of the metric system if amounts were given in grams as well. The discussion of the digestibility and absorption of foods is clear and sufficiently comprehensive and the same may be said of the important subjects of mineral and water metabolism. The consideration of Fletcherism and the work of Chittenden will strike most readers as fair, inclining as it does to the liberal side. There are many useful summaries of dietaries of armies, institutions and trainers. The remarks on alcohol will not please the total abstainer but will probably conduce to temperance. The directions for the treatment of various diseases are such as to be of great value to all. There are some omissions in these sections, as in leaving out the important work of Shaffer and Coleman in typhoid fever. The completeness of the work is shown by the discussion of vitamins though there is internal evidence in a certain unevenness that this chapter was written late. The errors in the spelling of proper names are unduly numerous and the index might be improved. On the whole the work is certain to be useful, and one factor in this is its convenient size and weight.

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TRANSIENT AURICULOVENTRICULAR DISSOCIATION WITH VARYING VENTRICULAR COMPLEXES CAUSED BY DIGITALIS *

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In 1913, Cohn¹ and Oppenheimer and Williams² described cases of heart-block in which the form of the ventricular complex showed frequent change

In Cohn's case the heart-block was transient On Aug 22, 1910, the patient showed partial heart-block with a 3-2 rhythm as shown by polygraphic tracings On Feb 10, 1911, this patient was studied again and showed a partial heart-block with a 2-1 rhythm On February 11 and 13 there was a complete auriculoventricular dissociation At this time electrocardiographic tracings were made and it was found that successive ventricular complexes changed their outline so that no two were precisely alike Two general types, however, could be distinguished, the one resembling the type of beat arising from stimuli originating in the wall of the right ventricle and the other those arising in the wall of the left ventricle Gradual variations were made out between these two types With the change in type there was also a change in interval between successive ventricular complexes This dissociation did not persist, for shortly after this time the rhythm was restored to a normal one Later examinations on Dec 19, 1911, and Feb 18, 1913, showed that the normal rhythm had been maintained except for an occasional premature ventricular contraction

This was a patient with cardiac decompensation, the etiology of which is not clear from the history It appears to have been a slowly developing myocardial insufficiency It seems not unlikely that the heart-block observed at the various times was the result of digitalis therapy

In the case of Oppenheimer and Williams the heart-block was permanent during the period of observation from Feb 26, 1912, to the day of the patient's death, Dec 31, 1912 Histologic examination of the heart, however, revealed no organic lesion to account for the

* Submitted for publication, April 7, 1915

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston

1 Cohn Heart, 1913, v, 5

2 Oppenheimer and Williams Proc Soc Exper Biol and Med, 1913, x, 86

block in the auriculonodal junction, the node of Tawara or the main stem and its branches. The nodal artery was sclerotic. The variations in the ventricular complexes were seen not only from one examination to the next but often from beat to beat. The waves Q, R, S and T all showed variations, for example in Leads 1 and 2 the R waves were sometimes upright and sometimes inverted. In Lead 3 the wave R was always inverted. The patient had marked Cheyne-Stokes respiration and the auricular rate was strikingly reduced during the dyspneic period, while the ventricular rate showed little change.

CASE 1—The patient was in the Peter Bent Brigham Hospital on two occasions, the first time (Peter Bent Brigham Hospital Medical No 426) from Oct 18 to Dec 18, 1913, the second time (Peter Bent Brigham Hospital Medical No 939) from March 11 to April 5, 1914, on which day he died.

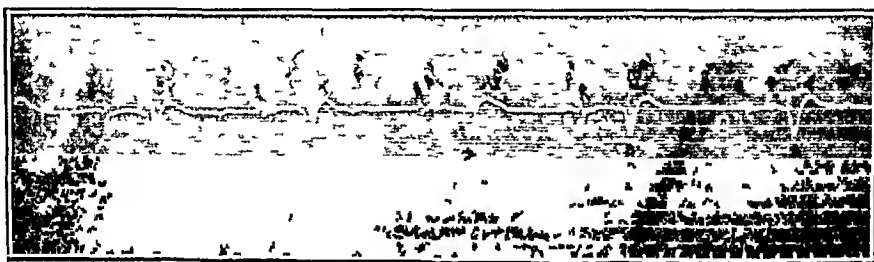


Fig 1, Case 1—Lead I, taken March 20, 1914



Fig 2, Case 1—Lead I, taken after Figure 1, March 20, 1914

The patient, a man aged 48, had been somewhat short of breath for the past two or three years, but not enough to keep him from his work, that of a barber. He had had more or less swelling of his ankles for ten years. During the winter prior to admission he had a chronic cough. About two months before admission he noticed that he was sleeping poorly and shortly after this his breath became very short, particularly at night, so that he was obliged to sleep sitting propped upright in bed. When he first entered the hospital the right border of cardiac dulness was at the right sternal margin, the left border 9 cm to the left of the midsternum. The apex beat was not seen or felt. Cardiac sounds were distant and a faint, blowing systolic murmur was heard, loudest at the apex. There were four or five beats of the same length followed by an extra beat, evidently an extra systole. The abdominal wall was edematous and brawny without shifting dulness. There was a brawny edema of the arms and legs.

The patient responded well to digitalis, and had a marked diuresis with disappearance of his edema. There was considerable evidence that in addition

to cardiac decompensation the patient had hypothyroidism With thyroid extract in addition to cardiac therapy he improved markedly and left the hospital Dec 18, 1913, in good condition, though unable to undergo much exertion

After leaving the hospital the patient remained at home on account of weakness and shortness of breath After a short time he became again very dyspneic and orthopneic, especially at night He had considerable cough and raised a small amount of frothy sputum Late in February, 1914, his feet began to swell About the middle of April his abdomen became prominent Symptoms of cardiac decompensation increased until he was readmitted on March 11, 1914, in an almost pulseless state

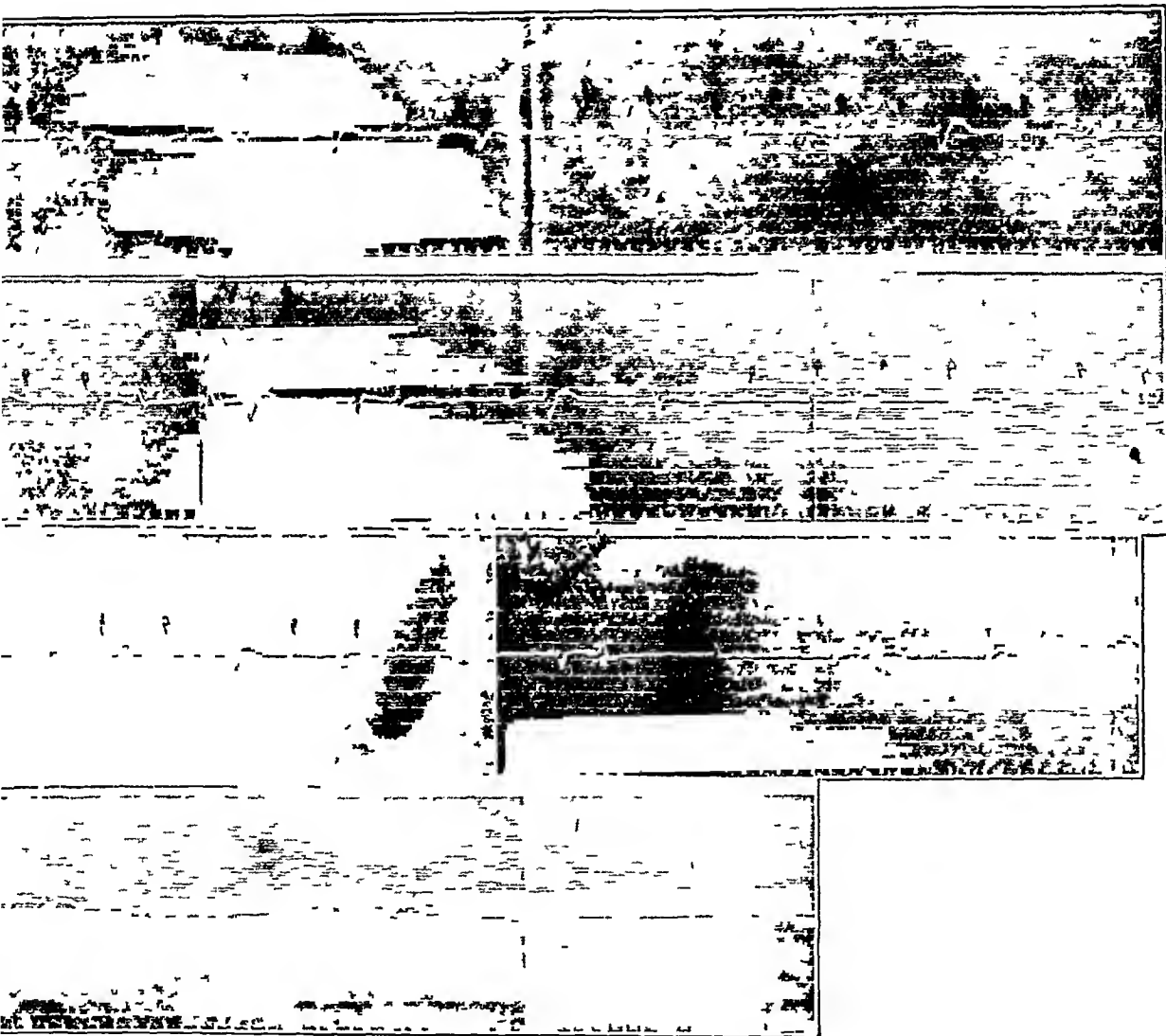


Fig 3, Case 1—Lead I, March 21, 1914 The strips form a continuous record

On March 11 physical examination showed the patient lying propped up in bed, moderately dyspneic and cyanotic with moderate edema of the legs below the knees and moderate edema of the abdominal wall and of the thorax as high up as the nipples The apex beat of the heart could not be felt The borders of cardiac dulness were made out with great difficulty owing to hyperresonance of the chest Heart sounds at the apex were barely audible, at the base the sounds were a little more distinct but were heard with great difficulty No murmurs were heard The heart action was regular No pulse could be made out at the wrist The lungs showed dulness at both bases with a few moist râles The abdomen showed shifting dulness The liver was enlarged, tender and pulsating On March 12 the patient had gradually

improved, his respiration had become Cheyne-Stokes in type but he was less dyspneic. On March 14 the patient had improved further and there had been marked diuresis with appreciable diminution of the edema of the extremities and the ascites. The heart sounds were stronger, still there was no murmur. On March 17 a systolic murmur was heard over the whole precordium. By April 2 the patient's condition had grown less good. He seemed stuporous. There was marked Cheyne-Stokes respiration. On April 4 he had grown distinctly worse and on April 5 he continued to fail and died at 4 45 a m. The cardiac condition had been regarded as one of chronic myocarditis in an individual with moderate hypothyroidism and moderate chronic nephritis.

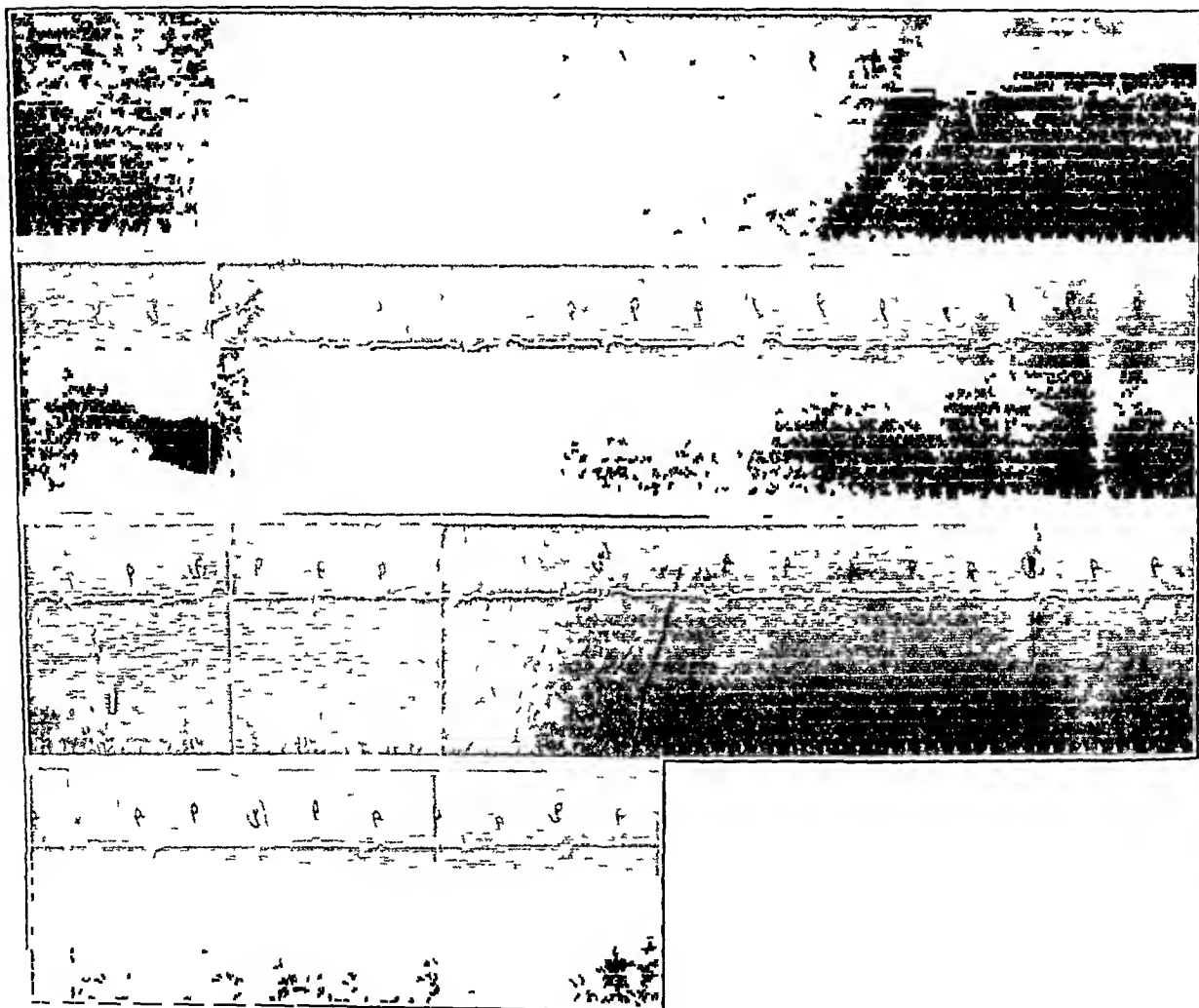


Fig 4, Case 1—Lead II, March 21, 1914. The strips form a continuous record.

During the second period in the hospital electrocardiographic studies were made. Some electrocardiograms taken on March 20 showed complete dissociation³ with an auricular rate of 78, a ventricular rate of 66, with paired ventricular beats coming in quite a regular relation to each other (Fig 1), the first one of the pair appearing to have its origin in the bundle of His, and the

3 In these cases the curves have been interpreted as showing complete dissociation. They might be interpreted instead as partial block with "P" waves at times in close association with ventricular complexes because contractions originating below the auricles have stimulated auricular contractions instead of the auricles and ventricles beating entirely independently of each other.

second one to have its origin in the ventricle. This condition, however, did not persist constantly, inasmuch as in some leads there was no pairing of beats in a regular sequence, while in others (Fig 2), both auricular and ventricular rates were quite regular though completely dissociated and all ventricular complexes were of supraventricular origin.

On the next day, March 21, the same general appearance persisted (Figs 3, 4 and 5) though there was greater variation in the form of the various ventricular complexes. There was a distinct tendency to an alternation of the character of the paired beats, in which the first ventricular complex of the

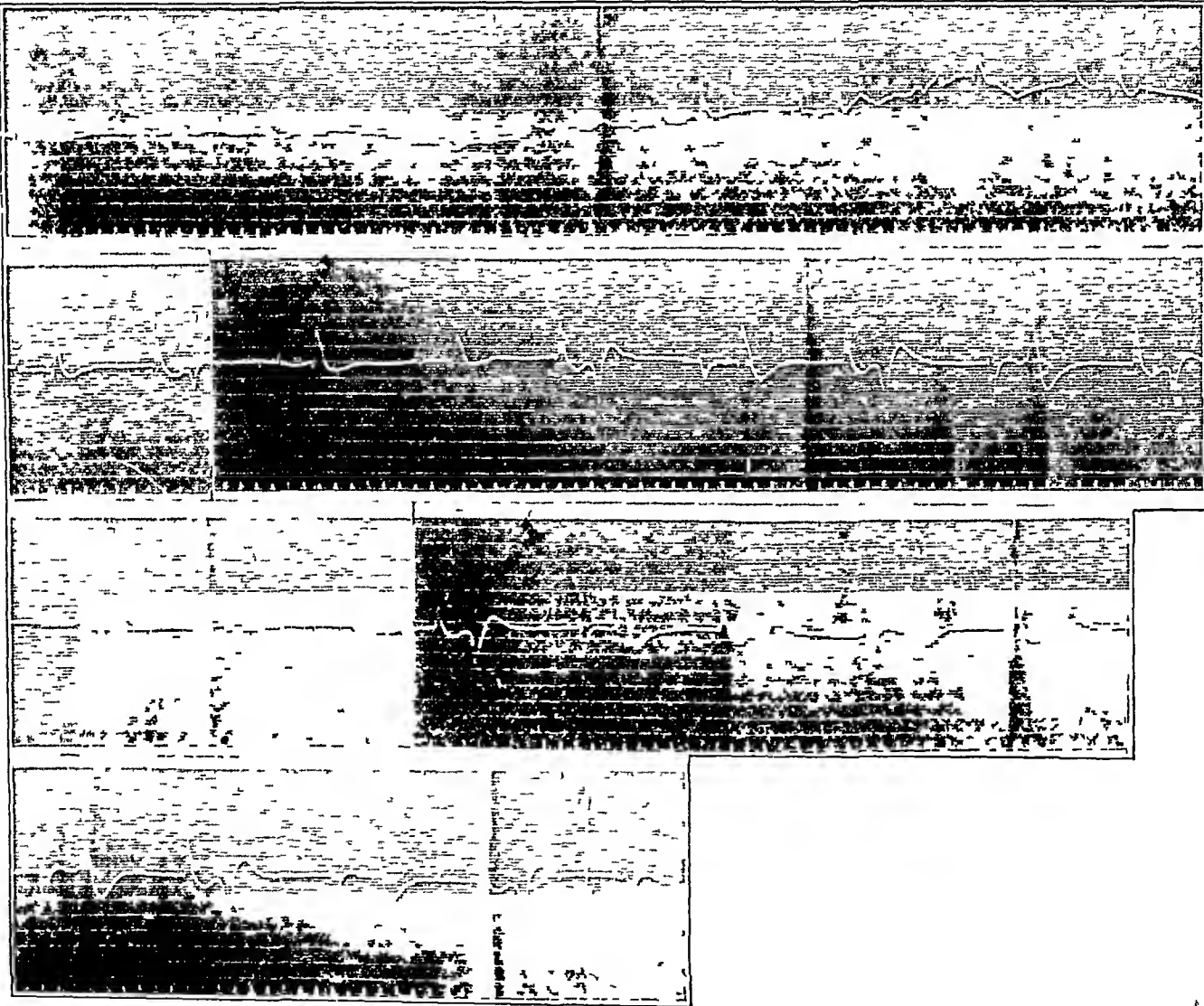


Fig 5, Case 1—Lead III, March 21, 1914. The strips form a continuous record except for a short break in the third strip.

pair gave an upward curve, and the second one a downward curve, and this arrangement changed in the next group so that the first complex was down and the second one up, and there was a considerable tendency to a regular alternation in this arrangement. In addition there were frequent minor changes in ventricular complexes as they succeeded each other, so that a great variety of complexes appear in any given curve.

The curve taken on March 25 showed a perfectly regular rate of 90, with all impulses transmitted from auricle to ventricle and ventricular complexes of normal form. There was a considerable delay, however, in the "P-R" interval, which reached its maximum on the next day, March 26, and then gradually

decreased, though never came quite to the normal time of transmission. The heart rate increased to 90 on March 26, to 104 on March 27, to 108 on March 28, and to 120 on March 30, and with this increase in rate of contractions the heart remained regular, the complexes normal in form, but the "T" and "P" waves gradually approached nearer and nearer until they became superimposed, which feature was very well shown by some curves taken on March 30, in which, following vagus irritation, there were some greatly increased intervals between successive "R" waves, and during these the "T" and "P" waves became separated (Fig 6)



Fig 6, Case 1—Lead II, March 30, 1914. Curve shows a pause caused by vagus pressure

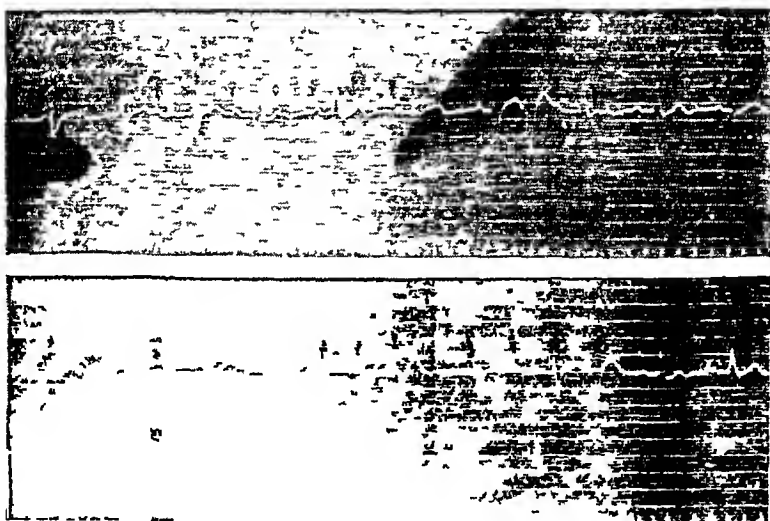


Fig 7, Case 1—Lead I, April 3, 1914. The two strips form a continuous curve and the second one is continuous with the curve in Figure 8

On April 2, though still regular, the rate of the heart slowed down to 84, and the "P-R" interval increased slightly in length.

On April 3 heart-block again occurred with an auricular rate of 126 and a ventricular rate of 72. In Lead 1 (Figs 7 and 8) this was present throughout, and at times there was such a pairing of the ventricular beats and changes in ventricular complexes as occurred when the heart was previously in block on March 20 and 21. This block, however, was not maintained, because in the interval between taking Lead 1 and Lead 2 the ventricular rate increased to 120, the ventricular complexes became normal in form, the "T" and "P" waves coincided (Fig 9). This condition persisted while Lead 3 was being taken. After Lead 3 was taken, Lead 1 was again taken, and at this time there was an auricular rate of 120 and a ventricular rate of 60, a partial heart-block with 2-1 rhythm. There was a "P-R" interval when transmission was not blocked varying between 0.2 and 0.24 of a second.

April 4 electrocardiograms showed a rate of 120 in Lead 1 with a superimposed "P" and "T" wave, and a "P-R" interval of 0.24 to 0.28 of a second. At one point in this curve there was a blocked auriculoventricular transmission and a pause of about double the length of the preceding intervals between "R" waves. Lead 2 on April 4 showed no blocking, whereas Lead 3 (Fig 10) showed a complete block and an auricular rate of 120 and a ventricular rate of 60. This apparently was not a partial block but a complete one, notwithstanding the fact that the auricular rate is twice that of the ventricular. This is brought out by the great variation in the time interval between the beginning of the "P" wave and the beginning of the next following "R" wave. At first glance, however, it would seem to be a partial block, with a 2-1 rhythm, the first beat not followed by a ventricular contraction, and the second beat fol-

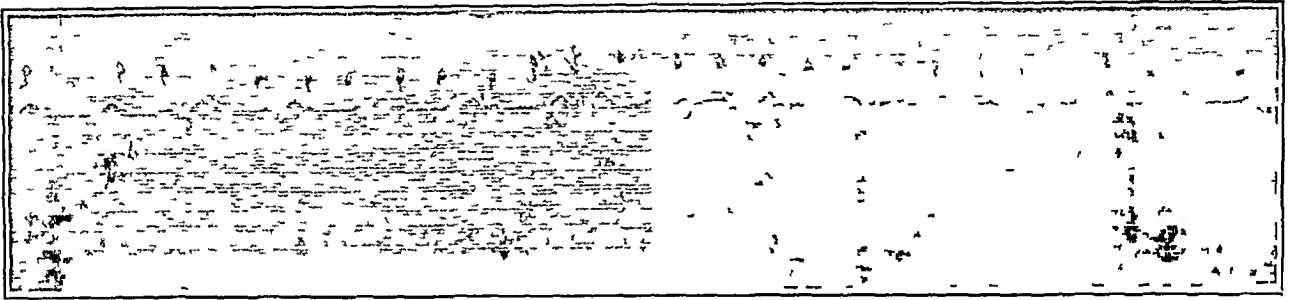


Fig 8, Case 1—Lead I, April 3, 1914. This strip is continuous with the second strip in Figure 7.

lowed by a ventricular contraction. Here again changes in form of ventricular complexes occur. A little later another tracing was taken which in Lead 1 shows a ventricular rate of 66 with an apparent complete block, however, the "P" waves are not distinct enough to justify any definite statement. Leads 2 and 3 have an auricular rate of 114 and a ventricular rate of 72. The complete blocking is much more evident as shown by the variations in conduction time.

The patient died during the night following these last tracings and at necropsy the heart showed the following condition:

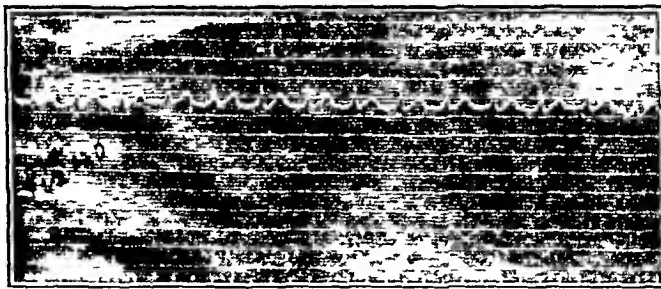


Fig 9, Case 1—Lead II, April 3, 1914. Curve taken almost immediately following that shown in Figure 8.

Heart Weight, 560 gm. In situ the heart borders measured 5 cm to the right and 11 cm to the left (horizontal measurements) of the midline. The right auricle was slightly dilated. The appendages were free. The pericardium was everywhere glistening. The tricuspid valve measured 12.5 cm. The line of closure of valves showed no abnormalities, the valves everywhere were delicate. The chordae tendineae were not thickened. There was slight dilatation of the right ventricle and the endocardial surface was everywhere glistening, showing no abnormalities. The wall measured 6 mm. The pulmonary valve measured 8.5 cm, the semilunar cusps were normal, the line of closure of cusps showed no roughening. The pulmonary artery was incised in situ, it showed no clots. There was a small amount of clot in the chambers above

described. The left auricle was not dilated. The auricular appendage contained a small irregular mass of fibrinous material, very fragile, this was somewhat whiter than normal but apparently was clot. The mitral valve measured 11.65 cm. The valve was thickened throughout. The chordae tendineae were somewhat thickened. There was no apparent change along the line of closure though superficially it was roughened. The wall of the left ventricle measured 1.6 cm. In the region of the septum, about 4 cm. below the aortic valve, was a mass which extended down to the apex, it being 4 cm. in length, adherent to the endocardium, irregular in outline, reddish in color and covered by a definite thin whitish membrane. The heart muscle was dark red in color, was of fairly good firmness, on cross section it was homogeneous and did not show macroscopic

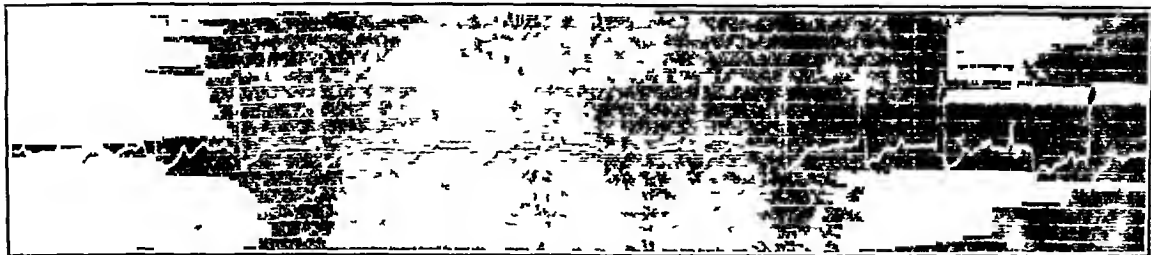


Fig 10, Case 1—Lead III, April 4, 1914

increase in connective-tissue elements. There was definite thickening of the endocardium, especially of the left auricle.

Coronary arteries. The orifices were open. There was marked thickening of the walls of the vessels, this was most marked down to the level of the bifurcation of the transverse and descending branches. In portions the lumen was practically obliterated. The walls were firm but not brittle. In one portion of the left anterior coronary there was apparently total obliteration of the lumen. Sections of heart muscle taken for microscopic study showed no interstitial fibrosis. There was no evident lesion of the conduction system.

CASE 2.—In this case the patient was in the Peter Bent Brigham Hospital (Medical No 1717) from Oct 3, 1914, to Nov 29, 1914, on which day she died. The patient was a woman, aged 29, who about seven months before admission, while in the seventh month of pregnancy, began to be troubled with



Fig 11, Case 2—Lead I, Nov 23, 1914, 9 25 a m

shortness of breath and soon became unable to lie down flat on account of dyspnea. About three weeks after this onset she went into labor and was delivered of a stillborn child. After remaining in bed for two weeks she got up and went about her work though she felt very weak. One month later she developed bronchitis attended with cough and expectoration, at times blood tinged. She began to have palpitation about three months before she came to the hospital and her feet began to swell, the swelling gradually extending up her legs. About three weeks before admission the swelling had involved her abdomen. Notwithstanding these symptoms she had remained up doing her housework as best she could.

When she entered the hospital, Oct 3, 1914, she was moderately dyspneic and her lips and skin were somewhat cyanotic. She had marked edema of the legs, moderate edema of her forearms, marked edema of her abdominal wall and the lower part of the thorax. Her abdomen contained fluid. There appeared also to be a moderate amount of fluid in each thoracic cavity. The right border of cardiac dulness was 5 cm to the right of the midsternal line, the left border 16 cm to the left of the midsternal line. The heart action was rapid and regular with a distinct presystolic gallop rhythm over the base. There was a short systolic murmur heard in the apex region. The pulmonic second sound was markedly accentuated. The systolic murmur present on admission at times disappeared, though it was usually present. Her condition grad-

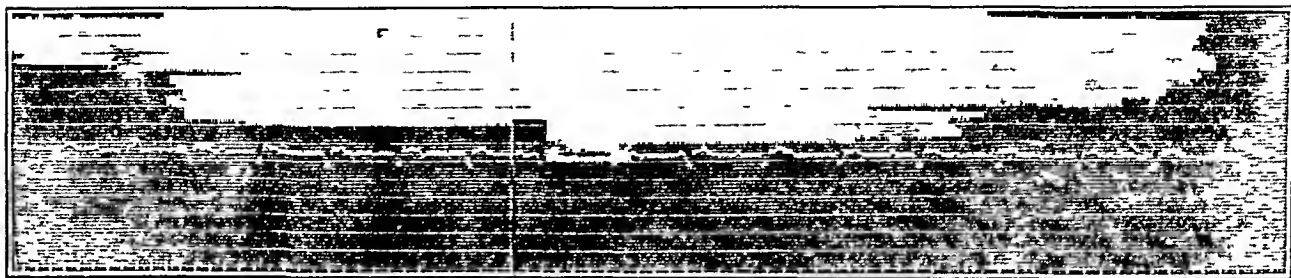


Fig 12, Case 2—Lead II, Nov 23, 1914. Record taken very shortly after that shown in Figure 11

ually improved, then remained stationary with a varying amount of edema. She received digitalis from time to time with no very marked effect on cardiac rate or rhythm except in the period beginning on November 22 in the afternoon. Up to the day of her death her general condition had not very essentially changed from that at the time of her admission. On November 29 she appeared as usual sitting propped up in bed, and was brightly talking to her neighbors when she suddenly died. We had considered the condition clinically as chronic myocarditis. No necropsy could be obtained.

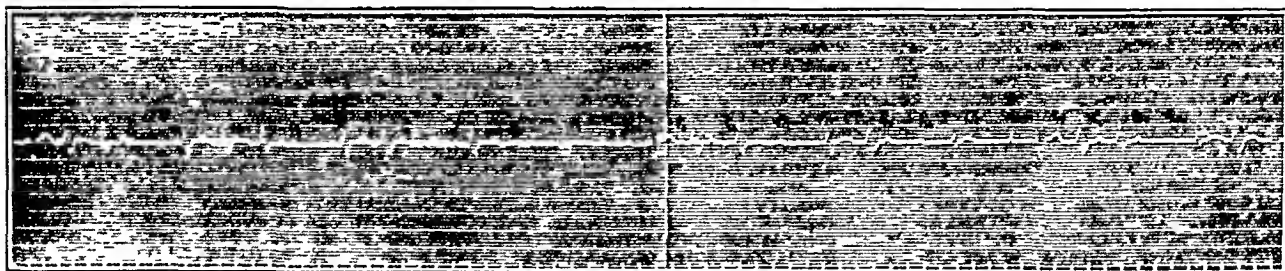


Fig 13, Case 2—Lead I, Nov 23, 1914, 9 45 a m

During her stay in the hospital electrocardiographic studies were made. From October 4 to November 22 numerous electrocardiograms showed essentially the same type of tracing with a "P-R" interval of about 0.16 of a second and normal except for a contour of ventricular complexes indicating a moderate degree of right ventricular hypertrophy. During all this period the patient had taken a considerable amount of digitalis as mentioned above, without any very definite effect of any kind except occasional nausea, at which time the digitalis was stopped.

On November 22 after having been on 10 c c of an infusion of digitalis three times a day from November 11 to 16, and four times a day from November 16 to 21, on which day the dose was increased in the afternoon to 12 c c four times a day, the patient became nauseated at 4 30 p m, and the digitalis was omitted.

Electrocardiograms were taken on the morning of November 22 and were similar to those taken on the preceding days. That afternoon the pulse fell from 110 to 90 and in the evening to 60, which was its rate next morning, November 23. An electrocardiogram was taken at 9 15 a m November 23, and showed at this time a rate of 93 with a long "P-R" interval, at times 0.34 of a second, in Lead 1. In Lead 2, taken a short time after Lead 1, the "P-R" interval had decreased to 0.22 of a second in the first part of the lead. In the latter part of the curve it lengthened out and there was a blocked impulse followed by two ectopic ventricular beats with blunt notched downward waves. In Lead 3 conduction time was similar to the first part of Lead 2. Ten minutes later there was complete auriculoventricular dissociation with an auricular rate

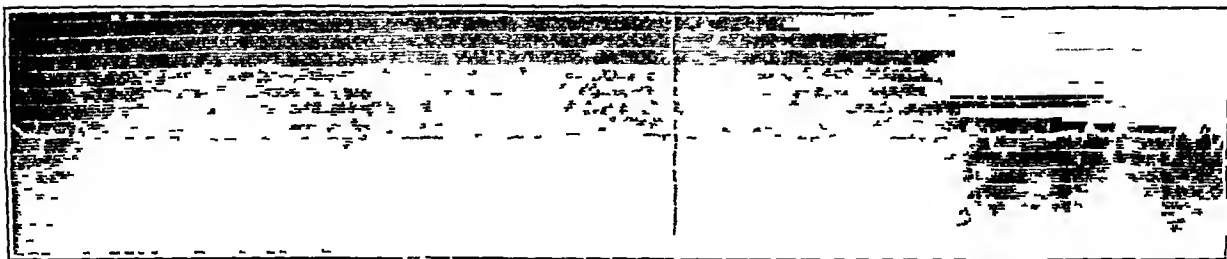


Fig 14, Case 2—Lead III, Nov 23, 1914. Record taken shortly after that shown in Figure 13.

of about 99 and a ventricular rate of about 70. In Lead 1 (Fig 11), succeeding ventricular complexes showed a change from complex to complex with two general types of waves, one with a moderately high "R" wave and a very slight "S" wave, the other with a slightly higher "R" wave and an "S" wave nearly as great as the "R" wave. In Lead 2 (Fig 12) there appeared with persisting complete dissociation a succession of broad notched downward waves in the ventricular complex, in form suggesting defective conduction in the right

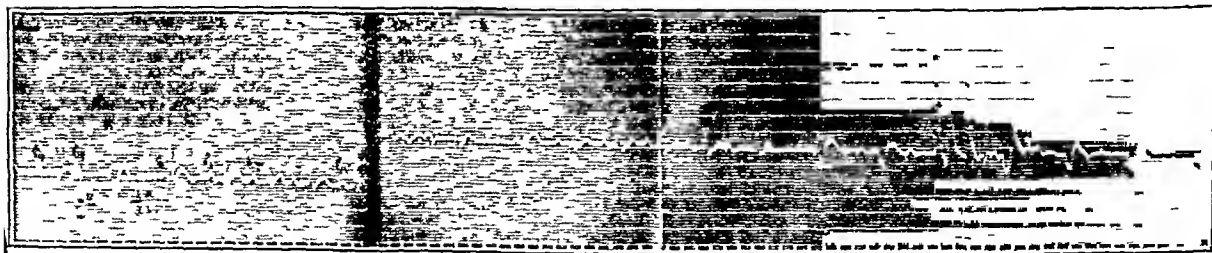


Fig 15, Case 2—Leads I and II, Nov 23, 1914, 3 p m.

branch of the bundle of His. After a brief interval another record of Lead 2 showed an admixture of ventricular complexes similar to those just described with complexes of normal supraventricular origin or with origin in the junctional tissue. Apparently complete dissociation had been maintained. In Lead 3 most of the ventricular complexes were of normal contour but there were occasional ones in which most of the complex was made up of a rather large downward deflection instead of the usual upward deflection. These downward deflections were not blunt or notched. Twenty minutes later complete dissociation apparently had persisted with now a larger number of ectopic beats in all three leads (Figs 13 and 14), giving a considerable variation in the type of succeeding complexes.

At 3 p m on November 23 the curve in Lead 1 (Fig 15) was very similar to that which was obtained at 9 25 a m on the same day, but the rate was slightly

more rapid. In Leads 2 (Fig 15) and 3 (Fig 16) there were considerably more ectopic ventricular beats of apparently various points of origin, and at places these occurred in rapid succession so as to suggest in places temporary ventricular fibrillation.

On the next day, November 24, at 11 a m, at 3 45 and at 3 50 p m the rate was regular and the complex similar to those during the early stay in the hospital, while at 4 p m it had become irregular with one or two ectopic beats following the normal beat, consequently a bigeminal or trigeminal (Fig 17) rhythm.

On November 25 and 26 no electrocardiograms were taken but the heart action judging by the pulse as felt appeared to be normal. On November 27

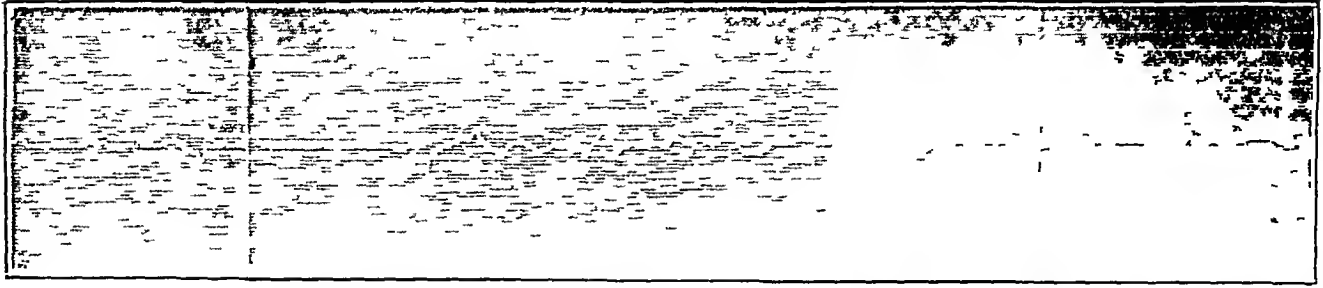


Fig 16, Case 2—Lead III, Nov 23, 1914, 3 p m

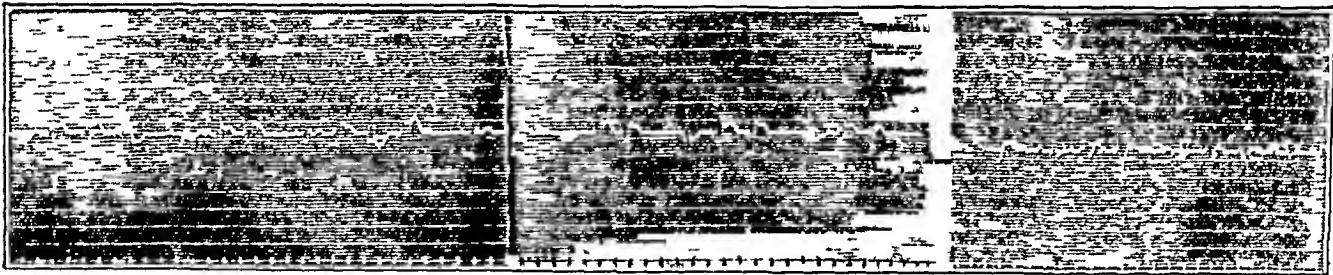


Fig 17, Case 2—Lead III, Nov 23, 1914, 4 p m

a normal curve was obtained. No others were taken between this time and the death of the patient on November 29 but in this period no pulse irregularity was noted.

CASE 3—In this case the patient was in the Peter Bent Brigham Hospital (Medical No 2043) from Dec 15, 1914, to March 9, 1915, on which day death occurred. This patient was a woman, aged 58, who about Christmas time,



Fig 18, Case 3—Lead I, March 5, 1915

1913, had a rather severe attack of indigestion and shortness of breath. She appears to have had similar symptoms for some time prior to this but never to such a marked degree. At this time dyspnea was severe enough to cause her to remain sitting up in a chair throughout the night. Under treatment she

improved so that she was in good condition until the middle of September, 1914, when the symptoms of Christmas, 1913, reappeared and in addition her legs swelled. These symptoms gradually increased and she became much weaker and feebler and lost considerable weight. When she came to the hospital her area of cardiac dullness extended 3 cm to the right of the midsternal line and 16 cm to the left. The heart rate was occasionally interrupted by extra systoles. No murmurs were heard. Her systolic blood pressure was 250. There was marked edema of the legs, abdomen and the lower back. Her eyes showed the picture of albuminuric retinitis. She had the urine of a chronic interstitial



Fig 19, Case 3—Lead II, March 5, 1915

nephritis and functional tests showed that this was of an advanced degree. She gradually grew worse and died on March 9. Clinically it had been a case of chronic interstitial nephritis, hypertension, heart hypertrophy and chronic myocarditis. No necropsy could be obtained.

Electrocardiographic study on Dec 16, 1914, showed the ventricular contour of a marked degree of left ventricular hypertrophy with a moderate number of ectopic beats of both auricular and ventricular origin. Electrocardiograms



Fig 20, Case 3—Lead III, March 5, 1915

on December 18 showed only ectopic auricular beats. Other electrocardiograms showed no ectopic beats. On March 1, 1915, electrocardiograms showed a typical picture of auricular fibrillation with no ectopic beats. On March 5, 1915, electrocardiograms showed at times a variety of ventricular complexes (Figs 18, 19 and 20), often changing in contour from beat to beat. In this curve no definite "P" waves could be made out though in places there were suggestions of "P" waves. The ventricular rate was regular as compared with the curve of March 1 when there was definite auricular fibrillation. Con-

sequently it cannot be said definitely what was taking place in the auricles. It may be that there was auricular fibrillation with a regular idiopathic ventricular rate or it may be that the auricles were beating and auriculoventricular dissociation was present, but the curves did not give distinct evidence of this.

During the early part of the patient's stay in the hospital she had had from time to time small amounts of digitalis. From January 29 to March 2, no digitalis was given. On March 2, 8 c.c. of an infusion of digitalis was begun at 10 a.m. and continued three times a day until 7 p.m. on March 5 when it was omitted owing to the character of the electrocardiographic record obtained on that day. The general condition of the patient was growing much worse during and prior to this period of digitalis therapy. Only one electrocardiographic record was taken after March 5. It showed auricular fibrillation without ectopic beats. This was taken on March 8 slightly less than twenty-four hours before the death of the patient.

CASE 4—In this case (Medical No. 2361) the patient was in the Peter Bent Brigham Hospital from Feb. 18, 1915, to March 18, 1915, on which day he was discharged. This patient, a man aged 68, about a year before admission began to notice that he was short of breath. Gradually this grew worse and he developed a cough with tenacious sputum. A distressed feeling in the region of his stomach with failing appetite and constipation ensued. No edema of his legs, however, developed. When he came into the hospital the area of cardiac dulness extended 3 cm. to the right and 14 cm. to the left of the midsternal line. A soft systolic murmur was heard at the apex and the heart sounds were fairly strong. The rate was moderately irregular of the extra systole type of arrhythmia as judged by the finger. The systolic blood pressure was 165 and the radial arteries showed pronounced sclerosis. In the bases of the lungs there were many coarse râles. The liver was slightly enlarged. No subcutaneous edema was made out. The case was regarded as one of chronic myocarditis and chronic nephritis. The patient improved in the hospital and was discharged in good condition. He received 5 c.c. of an infusion of digitalis three times a day from February 24 to February 27.

Electrocardiograms on February 18, 20, 23 and 24 showed a moderate number of ectopic beats of both auricular and ventricular origin and the ventricular complex of left ventricular hypertrophy. Pulsus alternans was present. On February 26, having started on digitalis on February 24 as previously described, the electrocardiograms showed the varying type of ventricular complex which has been described in the previous cases. However, the variations in type of ventricular complex were far less marked than in the cases previously described. The relation of auricular to ventricular beat could not be made out very satisfactorily as the "P" waves were indistinct. However, in places the "P" wave came very close to or was partially incorporated in the "R" wave so that it seems reasonable to suppose that the relation of the contraction of the auricle to the ventricle was similar to that in the previously described cases. On the next day there were found slight variations in some of the succeeding ventricular complexes. Subsequently on March 1, 5, 10, 12 and 13 the electrocardiograms were similar to those of the first days in the hospital.

Cohn offers three possible explanations for the varying ventricular complexes met with in his case. The first assumes a single permanent site in the main stem of the conduction system, above its division into right and left branches, as a source of stimulus to production and that this site is supposed to discharge impulses at regular intervals. Under this assumption the impulses are conducted now in one branch of the system and now in the other, the varying ventricular complexes depending on which branch the impulse traverses. The passage of the

impulse over one branch would, according to this interpretation, be the result of a temporary functional disturbance in the other. It assumes that complete dissociation between the contraction of the auricle and ventricle may be present as a temporary derangement, probably toxic, in the conduction system. The derangement must be of such a nature that impulses could not be conducted from auricles to ventricles, but could be conducted along that portion of the system in continuity with the ventricles, that is to say the portion between the A-V node and the distribution to the ventricular muscle.

The second explanation assumes that the site from which the impulses to contraction come is not fixed, but wanders from one side of the heart, that is to say of the conduction system, to the other. Cohn thinks that impulses so widely scattered as would have to be assumed here may give rise to an orderly succession of contractions, but that such an occurrence is unlikely.

The third explanation assumes that the stimuli to contraction arise synchronously or almost synchronously in the auricle and in the wall of the left ventricle, but the existence of block in Cohn's patient makes this unlikely. On the whole Cohn favors an intoxication as the basic cause of the phenomenon of varying ventricular complexes, assuming that his patient had digitalis intoxication.

Oppenheimer and Williams suggest in their case that the divergent types of ventricular complexes arise from the fact that the intrinsic ventricular pace-maker was frequently shifting or that the different impulses started at the same point and traveled either along different routes or at varying rates along the same route. As they found no anatomic lesion in the auriculoventricular system in their case they say that the heart-block may possibly be of neurogenic or circulatory origin or may be ascribed to chemical agents, to asphyxia or to some hindrance of the passage of impulses from terminal arborizations of the conduction system to the ventricular musculature.

In the cases which I have described variation in form of ventricular complexes was present similar to that described in the cases of Cohn and Oppenheimer and Williams, though not so marked in degree. In addition in my first case there was pairing of beats, a well-recognized digitalis phenomenon. My first patient had received digitalis from March 11 to March 15 in doses of 0.1 gram of powdered leaves every four hours and again from March 30 to April 4 in doses of 0.1 gram of powdered leaves four times a day. The first electrocardiograms taken on this patient were taken on March 20, five days after digitalis was stopped. These and those taken the following day showed the changing ventricular complexes. Subsequently normal cardiac rhythm was restored. On April 3, however, under digitalis therapy the phe-

nomena which occurred on March 20 and 21 reappeared. At necropsy the heart showed no evident lesion of the conduction system, and during life the blocking had been transitory. In my second, third and fourth cases the patients developed these changes under digitalis therapy and the condition was again transient. So it would seem that in my cases as well as in the others the variations in form of ventricular complexes were the result of digitalis action in individuals with hearts decompensated from myocardial insufficiency. Auriculoventricular dissociation developed as a result of digitalis and there was a further disturbance in conduction or in myocardial irritability leading to changing ventricular complexes. It is interesting in this connection that in my second case with auriculoventricular dissociation there appeared temporarily to be defective conduction in the right branch of the bundle of His in addition to the block higher up.

SUMMARY

As an occasional result of digitalis there develops a cardiac disturbance consisting of variations in the form of succeeding ventricular complexes. Of the cases, one reported by Cohn, one by Oppenheimer and Williams and four by myself, all except possibly one of my cases showed auriculoventricular dissociation³. In one of my cases the curve obtained did not justify any statement as to auricular activity, there may have been a regular rate in the auricles with auriculoventricular dissociation. All cases were of the type of chronic myocarditis without any marked signs of valve lesions.

Peter Bent Brigham Hospital

THE INACTIVATION OF PEPSIN BY SODIUM CHLORID ITS CLINICAL SIGNIFICANCE *

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The problem of the etiology of ulcer of the stomach has recently been approached from the point of view of that older problem—the nondigestibility of the stomach by its own digestive juice. For instance, Frentzel,¹ in 1891, and Katzenstein,² in 1908, showed that living stomach and duodenum implanted in the stomach were not influenced in any way, while small intestine and spleen under similar conditions were promptly digested. Katzenstein believed that the resistance of the stomach and duodenum to peptic digestion was due to the presence in the stomach wall of a specific inhibiting body—antipepsin.

In a more recent contribution, Katzenstein,³ by reducing the antipepsin content of the stomach and blood (by methods not altogether clear), succeeded in producing chronic experimental ulcers in dogs' stomachs. He concluded that gastric ulcer is a sequence to a local injury of the stomach wall, whereby the normal balance between gastric juice pepsin, and gastric wall antipepsin, is disturbed.

While these conceptions are interesting and original, considerable doubt has arisen as to the validity and nature of this so-called antipepsin. Carl Oppenheimer, in his "Die Fermente und ihre Wirkungen,"⁴ after a critical survey of all available evidence, concludes

Im Allgemeinen ist es wohl wahrscheinlich dass hier keine echten Antikörper im Sinne der Immunitätslehre vorliegen. Es sind eher negative Katalysatoren.

He points out that this antipepsin is thermostabile, that it does not completely inhibit pepsin action, and that similar "antipepsins" may be found in extracts of yeast, molds and bacteria.

During the progress of research⁵ on so-called antipepsin of the blood serum in 1911, I was able to show, in association with Dr Jobling, that blood serum is capable of permanently binding pepsin and preventing it from digesting protein. We concluded from a con-

* Submitted for publication May 2, 1915.

* From the Morris Institute for Medical Research and the Michael Reese Hospital, Chicago.

1 Frentzel (quoted by Kathe) Berl klin Wchnschr, 1908, xlv, 2136.

2 Katzenstein Berl klin Wchnschr, 1908, xlv, 1749.

3 Katzenstein Arch f klin Chirurg, 1913, ci, 1.

4 Oppenheimer, C "Die Fermente und ihre Wirkungen," Ed 3, Leipzig, 1910.

5 Hamburger Jour Exper Med, 1911, xiv, 535.

siderable series of biochemical experiments that this inactivation of pepsin was not due to a specific antibody of the blood serum, but was due to a quantitative *nonspecific* pepsin deviation, similar to the deviation described for other ferments, notably trypsin

In the development of a suitable technic for this work, a most interesting fact was observed, notably, that under certain conditions, sodium chlorid, used as physiological salt solution, would completely prevent pepsin from digesting protein. The conditions under which this inhibition occurred are simply that the ferment be made up in aqueous solution, with all trace of hydrochloric acid removed. If a faint trace of acid be present, or be added before sodium chlorid solution, no inhibition occurs. Moreover, hydrochloric acid added

TABLE 1—INHIBITION OF PEPSIN BY SODIUM CHLORID

Tube *	0.85 Pct NaCl cc	Water cc	N/10 HCl cc	10 Minutes	60 Minutes	18 Hours	24 Hours
1	25		0.5	0	0	0	0
2	25		1.0	0	0	0	0
3	25		5.0	0	Trace?	0	0
4		25	0.5	0	+	+++	++++
5		25	1.0	0	+	+++	++++
6		25	5.0	0	+	++++	++++
7			0.5	0	+	+++	++++
8			5.0	0	+	++++	++++
9			1.0	0	+	++++	++++

* In each tube was placed carmin fibrin and 0.0001 gm pepsin in 1 cc water. All tubes were incubated for thirty minutes.

Sodium chlorid (25 cc of 0.85 per cent solution) prevents pepsin in solution in water from digesting carmin fibrin, the addition of N/10 hydrochloric acid in excess does not reactivate ferment. Control tubes alone and with water show complete digestion in twenty-four hours. 0 = no digestion, +, ++, +++, partial digestion, ++++ = complete digestion.

after sodium chlorid inhibition fails to reactivate the pepsin, the inhibition remaining permanent—*inactivation* (Tables 1 and 2 will make these relations clear). Under such conditions, sodium chlorid would likewise be considered an antipepsin.

It was our belief that this inactivation of pepsin (when in aqueous solution) by normal serum and by sodium chlorid were important factors in the action of so-called antipepsin, and that such inactivation was responsible for most, if not all, of the published accounts of antipepsin.

The inhibiting action of sodium chlorid on pepsin has been studied particularly by Schutz⁶ and Levites⁷. In a physicochemical study of

⁶ Schütz Beitr z chem Physiol u Path, 1904, v, 406

⁷ Levites Ztschr f physiol Chem, xlviii, 187

the inhibiting effects of various salts on peptic digestion, Schutz arranged a table of their anions and cations in a decreasing order of their inhibiting action

Levites, using other methods, came to practically similar conclusions, finding that the acid portion of the salt causes most active inhibition, that the metal portion was relatively slight, and that the salts of weak acids were more strongly inhibitory than those of strong acids

We found, further, that if pepsin was dissolved in an acid solution strong enough to prevent inactivation by sodium chlorid, simple neutralization of this acidity alone (without addition of sodium chlorid) sufficed to cause inactivation. This is caused by the sodium chlorid formed from interaction of acid and alkali acting in a neutral

TABLE 2—PROTECTION OF PEPSIN BY HYDROCHLORIC ACID AGAINST INACTIVATION

Tube *	Pepsin in 1 cc H ₂ O gm	Pepsin in 1 cc N/10 HCl gm	N/10 HCl cc	10 Minutes	30 Minutes	18 Hours	36 Hours
1	0.0001		0.5	0	0	0	0
2	0.0001		1.0	0	0	0	0
3	0.0001		5.0	0	0	0	0
4		0.0001	0.5	+	+	+++	++++
5		0.0001	1.0	+	+	++++	++++
6		0.0001	5.0	+	+	++++	++++

* In each tube was placed carmin fibrin and 2.5 cc 0.85 per cent sodium chlorid. All tubes were incubated for thirty minutes.

Sodium chlorid (2.5 cc in 0.85 per cent solution) prevents pepsin in solution in water from digesting carmin fibrin, in spite of the subsequent addition (in excess) of N/10 hydrochloric acid. Pepsin dissolved in N/10 hydrochloric acid is not prevented from acting by sodium chlorid.

solution to cause inactivation, the ferment having been placed in a neutral solution by this same interaction. This last fact—the inactivation of pepsin—by the neutralization of acid pepsin, forms the basis for this report, particularly the significance of this finding in the neutralization of gastric juice.

Gastric juice was obtained from Pawlow dogs and by aspiration of the human fasting stomach in seven cases:

Normal stomach

Alcoholic gastritis

Hyperacidity—two cases

Ulcer

Carcinoma—two cases

Peptic digestion was estimated by nitrogen determinations of the noncoagulable proteid of inactivated beef serum, after the method described in the work on antipepsin.

The following cases will serve as illustrations

CASE 1—B S, male medical ward Clinical diagnosis, gastric ulcer Aspiration of fasting stomach 20 c c bile-stained fluid, free hydrochloric acid 6, total acid 20

TABLE 3—INACTIVATION OF PEPSIN BY NEUTRALIZATION OF GASTRIC JUICE FROM ULCER PATIENT

Flask	Gastric Juice c c	Neutral- ized Gastric Juice	Neutral- ized and NaCl Added	N/10 HCl c c	Beef Serum c c	Kjeldahl
1	05	0	0	5	5	340
2	05	+	0	5	5	35
3	05	+	+	5	5	28

In Flask 1, the unchanged juice gave a digestion figure of 34 (Kjeldahl), while Flask 2, in which juice had been neutralized with tenth-normal sodium hydroxid, no digestion occurs (35 Kjeldahl resulting from control normal serum) In each flask the later addition of 5 c c hydrochloric acid fails to reactivate pepsin In other words, the ferment is *permanently* inactivated (deviated), and prevented from causing further digestion by the simple neutralization of the gastric juice

CASE 2—I S Male medical ward Clinical diagnosis, carcinoma Aspiration of fasting stomach 12 c c viscid yellow-green fluid, free hydrochloric acid, 0, total acid, 40

TABLE 4—INACTIVATION OF PEPSIN BY NEUTRALIZATION OF GASTRIC JUICE IN CARCINOMA OF THE STOMACH

Flask	Gastric Juice c c	Neutral- ized Juice	Neutral- ized and NaCl Added	NaCl	N/10 HCl c c	Beef Serum c c	Kjeldahl
1	05	0	0	0	5	5	188
2	05	+	0	0	5	5	30
3	05	+	+	0	5	5	46
4	05	0	0	+	5	5	177

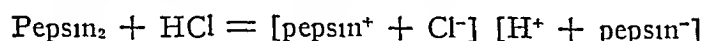
This case is similar to the preceding, showing in addition in Flask 4 the inability of sodium chlorid alone to deviate ferment

Although seven cases constitute a minimum number on which to draw conclusions, still the findings were so uniformly positive and so completely in accord with the earlier work, that it seemed unnecessary to gather a larger series They showed constantly that the neutralization of gastric juice results in complete inhibition of peptic action *even after the addition of hydrochloric acid in excess*, and that the inhibition of pepsin is due to *sodium chlorid acting in a neutral medium*

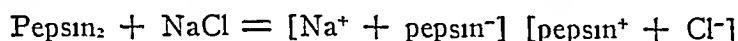
What is the mechanism of the inhibition of pepsin by sodium chlorid? While there is no direct experimental answer to this question, the explanation, I believe, rests on the modern conception of ferment action, as described by Michaelis,⁸ Loeb,⁹ and others

Michaelis, with the aid of electrical conductivity readings, found that the proteolytic action of pepsin depends on its electrolytic dissociation, and that only the positively charged pepsin ions (cations) are capable of proteolytic digestion

On the addition of hydrochloric acid to neutral pepsin, a salt is formed which may dissociate in one or both of two ways



Of these only the cation pepsin (*pepsin*⁺) is active. If, however, sodium chlorid be added in place of acid, a new salt is formed, sodium pepsin, which is proteolytically inactive because of the preponderance of inactive anions and absence of active cations



Has this phenomenon of pepsin inactivation any clinical application? If so, its significance would lie in the ability to adopt measures whereby the stomach acid could be completely neutralized and the neutral reaction continuously maintained, and also that the newly formed and secreted acid could be immediately and continuously bound with alkali, as soon as it was formed. If this could be accomplished, the pepsin set free by neutralization, as well as the newly secreted pepsin, would be bound by inhibiting sodium chlorid and permanently inactivated and deviated. As a result, peptic activity would be destroyed for a period of time equal to the continuance of the neutral reaction, a condition similar to achylia gastrica. In fact, the findings would be those of a temporary achylia, with neutral or alkaline reacting stomach contents and total absence of peptic digestion

Under what conditions would such a temporary achylia be desirable? First, as a prophylactic measure, to prevent the formation of gastric or duodenal ulcer. Second to facilitate the healing of ulcer by removing the factor which, next to mechanical trauma, is probably of greatest importance in the continuance and progression of chronic ulcer. Therefore, in simple hyperacidity, in hypersecretion from whatever cause, in motor insufficiency with continuous secretion, in pylorospasm with hyperacidity and hypersecretion, in chronic ulcer, in gastroenterostomy to prevent the formation of jejunal ulcer, neutralization with peptic inactivation might be desired

⁸ Michaelis and Davidsohn. *Bioch Ztschr*, 1911, xxxvi, 280

⁹ Loeb. *Bioch Ztschr*, 1909, xix, 534

The present methods of treatment of these hyperacid conditions with alkaline substances, attempt to control or lessen the chemical discomfort and to *reduce* the degree of acidity—particularly of the free hydrochloric acid. While such methods are of highest importance, it is evident, from these experiments, that the ideal of alkaline treatment is not merely the lessening of gastric acidity, but, of probably far greater importance, *the complete and continuous neutralization of the acid contents of the stomach*—to the end that pepsin be deviated and peptic digestion prevented.

The endeavor to demonstrate and maintain complete, continuous neutralization of the gastric contents is being made at the present time. By means of a Rehfuess stomach tube, kept constantly in the stomach for days at a time, fractional aspirations and readings of the stomach contents can be made at any time, and the degree of acidity or alkalinity measured. By this means, the effect of various foods, methods and time of feeding, neutralizing strength of various alkaline substances, can be directly measured and recorded. The results from these investigations are too few to warrant publication at this time. In general, however, it may be said that by the use and combination of certain of these alkaline substances, combined with certain foods and methods of feeding, continuous, complete neutralization of the stomach contents can be demonstrated and maintained.

CONCLUSIONS

1 Sodium chlorid will prevent pepsin in aqueous solution from digesting protein. This confirms the work of Schutz and Levites on the inhibiting action of various salts on peptic digestion.

2 The inhibition of pepsin by sodium chlorid, together with the ability of animal serum to deviate pepsin (described in an earlier paper), is responsible for most, if not all, of the published accounts of antipepsin.

3 The inhibition of pepsin by sodium chlorid is permanent, the inactivated ferment failing of reactivation by the subsequent addition of hydrochloric acid. The inactivation may be prevented, however, by dissolving the ferment in dilute hydrochloric acid.

4 Neutralization of pepsin dissolved in hydrochloric acid alone (without the addition of sodium chlorid) inhibits the ferment by the sodium chlorid formed from union of alkali and acid, acting in a neutral solution. Complete neutralization of the gastric juice causes similar pepsin inactivation.

5 The inactivation of pepsin by complete and continuous neutralization of gastric juice is indicated in the treatment of various diseases.

of the stomach in which temporary inhibition of peptic digestion is desired. This is particularly true in the prevention and cure of chronic gastric ulcer. By the use of certain foods, methods and time of feeding, and various alkaline substances, complete and continuous neutralization can be obtained.

104 South Michigan Boulevard

ENDEMIC TYPHUS FEVER IN THE PHILIPPINE ISLANDS

OBSERVATIONS BASED ON A STUDY OF TWENTY-THREE CASES OCCURRING
AMONG FILIPINOS AT CAMP KEITHLEY, MINDANAO, P I, WITH
THE RESULTS OF ANIMAL INOCULATIONS *

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Endemic typhus fever has not been reported, heretofore, as occurring in the Philippine Islands. Reference to the Reports of the Director of Health,¹ from July 1, 1911, to Jan 1, 1914, shows that occasional cases resembling typhus fever have occurred in Manila, but "not sufficient confirmatory evidence could be obtained as to the correctness of the diagnosis to warrant reporting them as typhus"

It is believed that sufficient data—clinical, laboratory and epidemiologic—are embodied in this report to show that typhus in endemic form unquestionably exists in the Philippines, at least in the Lanao section of Mindanao

Twenty-three cases have been studied in the military hospital at Camp Keithley. The first case, erroneously diagnosed as malaria, was admitted Aug 28, 1914. During September four additional cases were under observation, and it became evident that the disease was not one of those ordinarily encountered.

Tentative clinical diagnoses of typhus fever were made in these cases by elimination, but, in the absence of confirmatory laboratory evidence, the first positive diagnosis was not made until October 12.

The disease observed here corresponds to the acute infectious disease described by Brill² of New York which, subsequently, was proved by Anderson and Goldberger³ to be identical with the typhus fever of Mexico. In our cases the period of incubation appeared longer, the average leukocyte count was less and marked nervous manifestations—absent in Brill's cases—were not uncommon in ours.

* Submitted for publication March 19, 1915

1 Ann Rep Bureau Health, Philippine Islands, Dec 31, 1912, p 94, *ibid*, June 30, 1913, p 131, *ibid*, Dec 31, 1913, p 102

2 Brill, Nathan, E. An Acute Infectious Disease of Unknown Origin, a Clinical Study Based on 221 Cases, *Am Jour Med Sc*, April, 1910, p 484

3 Anderson, John F, and Goldberger, Joseph. The Relation of So-Called Brill's Disease to Typhus. An Experimental Demonstration of Their Identity, *Pub Health Rep*, Feb 2, 1912

Although in general our cases fall into the category of Brill's disease, an occasional case was encountered which approximated in severity the epidemic typhus of Europe. One case in particular was strikingly like a case of European typhus in an immigrant which I had the opportunity of observing clinically, and subsequently at necropsy at the Philadelphia Hospital for Contagious Diseases in 1906.

The disease does not coincide with the descriptions of the Manchurian typhus observed during the Russo-Japanese War, and the temperature curve, with its steep rise during invasion and abrupt decline, differs from the more gradual curve described as occurring in the typhus fever of Mexico.

The following general description fits the average case observed during this endemic. Variations from the usual picture were common and these will be considered as special features of the disease.

SYMPTOMS

The period of incubation in those cases in which it could be arrived at with any degree of certainty varied from ten to fourteen days. Prodromes were absent. The onset was abrupt, a chill ushering in the disease in twenty-one of our twenty-three cases. Headache, usually frontal, followed the initial chill quite constantly and invariably constituted the dominant symptom. In six cases vomiting occurred at the onset, and 25 per cent of those observed complained of backache and pain in the extremities. Fever immediately followed the onset. The temperature rose rapidly to 103 or 104 F and, reaching its fastigium on the second or third day, remained elevated, with morning remissions and evening exacerbations, for about a week. Defervescence, occurring in the usual case about the tenth day, was by crisis or rapid lysis through forty-eight hours. The pulse was full and bounding, relatively slow as compared to the fever and was not dicrotic.

The patient was seen within forty-eight hours after the onset as a rule. He was apathetic, and looked dull and stupid, but was not mentally confused. The face and neck were flushed or turgid, the temporal veins engorged and prominent and the conjunctivae injected. The bowels were either constipated or regular, there being no tendency to diarrhea. The lips were usually parched, sometimes fissured, and sordes on the lips and teeth was constantly noted in the severer cases. The tongue resembled that of typhoid fever, being coated along the dorsum and clean at the tip and edges. Early in the disease the tongue was swollen, moist and flabby, becoming dry and covered with a heavy brown coating later. The breath had a heavy musty odor not unlike that of typhoid fever. Nervous manifestations in the form of tremor of the hands, tongue and lips were present from the beginning.

Tremulous speech was less constant but not infrequent. Prostration and profound anorexia developed early.

About the third day the spleen could be palpated. On the fourth day subcuticular mottling, most marked in the dependent parts, was noted. The eruption was observed on about the fifth day, beginning on the abdomen and chest and rapidly spreading to the extremities. The so-called *tache cérébrale*—the appearance of a red line on the skin when stroked with the finger—was demonstrated constantly. It appeared early and could be elicited for several days after the eruption had disappeared. The headache and other subjective signs usually ameliorated on about the sixth day, and the patient became comparatively comfortable.

The crisis could be looked for on about the tenth day. Preceding the crisis the patient became restless and nervous and the brow was usually moist. Profuse sweating and diuresis were almost invariably concomitants of the crisis, while diarrhea and vomiting occurred occasionally. Following the crisis all symptoms ameliorated, the spleen receded and the eruption faded rapidly. More or less prostration was usual for twenty-four hours after the crisis, following which the tongue cleaned, the appetite returned and convalescence was established with a rapidity that was striking and all out of proportion to the clinical picture preceding it.

SPECIAL FEATURES

The *onset* was characterized by chill in twenty-one cases, headache in nineteen and by vomiting in six. Lumbar pain and pains in the extremities occurred in eight cases and vertigo was recorded once. In two of the cases the onset was gradual and fever was the first symptom noted. There was intense pain in the chest in one case at the onset, probably due to pulmonary congestion.

The *facies* at the onset was that of intense congestion—face flushed, temporal veins prominent and conjunctivae injected. The expression in some cases was anxious and in others dull and stupid. The color remained good until the crisis, after which pallor was evident for a variable time and the patient exhibited a “washed out” appearance.

The *temperature* rose rapidly during the stage of invasion, reaching the fastigium on the second to the sixth day. The average fastigium in twenty-one cases was 103.5 F, the lowest 102 F and the highest 104.6 F. The fastigium was reached on the third or fourth day in 50 per cent of the cases. In about two-thirds of the cases an initial drop or remission of from 3 to 5 degrees occurred on the second, third or fourth day. This single early remission occurred with sufficient fre-

quency to constitute a special feature of the temperature curve, and that it occurs, apparently, in typical cases of typhus fever, witness the temperature charts from Murchison,⁴ Wilson⁵ and Doty⁶

After reaching the fastigium the usual curve was that of continued fever, with morning remissions of a degree or two, until defervescence. The fever was distinctly remittent in five of our twenty-three cases, remissions of over 2 F occurring daily in these cases. An occasional case was encountered in which the fever was irregular and conformed to neither the continued nor remittent type. Defervescence was by crisis in fourteen cases, by rapid lysis in six, and in the remaining three cases the type was too doubtful to classify. A pseudocrisis followed by recurrence of fever occurred seven times. Pseudocrises were noted from the fifth to the twelfth days. Crises occurred from the fourth or fifth day, in mild or abortive cases, to the twelfth or fourteenth day in the severer cases. Lysis covered a period varying from forty-eight to ninety-six hours. The febrile period in this series of cases ranged from six to sixteen days, terminating from the tenth to the fourteenth day in the majority. The temperature was considered normal when the evening temperature reached 98.4 F. After defervescence the temperature usually oscillated for three or four days, remaining within a degree of normal, and then became subnormal for a period varying from two or three days to a week. Slight chills and chilly sensations, during the course of the disease, occurred in two cases.

The *skin* of the face, neck, upper part of the chest and of the back and shoulders was suffused during the early days of the disease. Sweating was unusual before the crisis, being noted but twice. Sudamina did not occur. Herpes labialis was observed in one case. The so-called *tache cérébrale* was a constant phenomenon. It could be elicited before the eruption appeared and after its disappearance. In eleven of the twenty-three cases the skin became mottled on the fourth or fifth day and the characteristic eruption followed.

The *eruption* occurred in sixteen cases, was absent in two cases and in the remaining five cases, which occurred during the first part of the endemic, the rash was either absent or overlooked. It appeared on the fifth day in two-thirds of the cases, but in isolated cases it was observed as early as the fourth day and as late as the eighth day. It appeared first on the abdomen and chest and, developing rapidly

4 Murchison, in Osler. Principles and Practice of Medicine, Ed 8, New York, D Appleton & Co, 1912, p 354

5 Wilson. Medical Diagnosis, Philadelphia, J B Lippincott Company, 1909, p 642

6 Musser. Medical Diagnosis, Ed 5, Philadelphia, Lea Brothers & Co, 1904, p 703

and not in crops, had extended to the back, shoulders, arms, hands, legs and feet and in two cases to the face within twenty-four hours. The lesions were discrete, slightly raised, rose-red to dark red, irregular in outline and measured from 2 to 8 mm in diameter. Some of the spots were hyperemic and disappeared on pressure, others darker red, were modified but not entirely blanched by pressure, while an occasional spot here and there was distinctly petechial, fading gradually after the eruption had disappeared and leaving dirty yellowish stains in the skin. In individual cases the lesions numbered from a few dozen to many hundreds. In the average case the spots were much more profuse than the rose-spots of typhoid and less numerous than the lesions in the average case of measles. The eruption faded rapidly with the crisis and had disappeared by the tenth day. Desquamation did not occur.

The *blood* showed certain constant changes. The leukocyte count, in sixteen cases, varied from 4,000 to 18,000, the average count being 7,865. Differential leukocyte counts showed a rather consistent increase in the percentage of large mononuclear cells, with a corresponding decrease in the number of polymorphonuclears. Eosinophils were not present in appreciable numbers during the febrile period. These observations are in accord with those of Wilson⁷ at Belfast, who states that a relative increase in the large mononuclears, especially toward convalescence, was very characteristic and that during the febrile period eosinophils were absent or scanty.

The average differential count in sixteen cases showed polymorphonuclears 55 per cent, lymphocytes 25 per cent, large mononuclears 16 per cent, eosinophils 0.8 per cent and basophils 0.2 per cent. Unfortunately, routine estimations of hemoglobin and red cell counts were not made. Clinically, however, there appeared to be anemia of varying degree following defervescence of the fever. In considering the blood changes, the fact should be mentioned that feces examination showed that the majority of the patients harbored intestinal parasites.

Blood cultures in fifteen cases gave negative results. Blood was taken from a vein, and flasks of plain broth or dextrose broth were inoculated at the bedside. Both aerobic and anaerobic cultures remained sterile after from three to ten days incubation at 37 C. In justice to the contention of Plotz,⁸ who recently reports having isolated an anaerobic organism from cases of typhus fever in New York, I confess that the technic employed in making anaerobic cul-

7 Wilson, W. J. The Etiology of Typhus Fever, *Jour Hyg*, August, 1910, quoted by Balfour and Archibald, Second Review, Wellcome Research Laboratories, Khartoum, 1911, p. 387.

8 Plotz, Harry. The Etiology of Typhus Fever and of Brill's Disease, Preliminary Communication, *Jour Am Med Assn*, 1914, lxii, 1556.

tures here was, of necessity, crude. Tubes of dextrose-broth were heated to drive off as much oxygen as possible, cooled rapidly, inoculated, and the surface of the medium was covered with a layer of sterile oil to exclude oxygen. Obviously, the degree of anaerobiosis obtained by this method was only relative, but more approved methods could not be resorted to with the facilities at hand.

The *pulse* exhibited no characteristic features. Early in the disease it was of good volume and tension, relatively slow as compared to the temperature, and diastole was absent. A pulse rate over 100, with the temperature ranging between 102 and 104 F, was the exception rather than the rule. The critical fall in temperature was occasionally

TABULATED RESULTS OF LEUKOCYTE COUNTS

Case No	Day of Disease	Leuko-cytes	Polymor-phonuclear Per Cent	Lympho-cytes Per Cent	Large Mononu-clears Per Cent	Eosino-phils Per Cent	Baso-phils Per Cent
1	4th	11,500					
1	7th	18,000	72	12	15	1	
8	7th	5,000	61	20	18	0	1
9	3d	6,600	68	23	15	1	
10	3d	8,400	77	12	11		
11	2d	8,000	50	23	25		
12	3d	5,000	25	25	50		
13	2d	10,000	45	39	15	1	
14	2d	5,000	57	30	12		
15	5th	4,000	65	25	9		1
16	4th	6,000	65	19	15	1	
17	6th	8,600	67	23	11		
18	5th	6,800	58	32	16		
19	3d	7,500	55	35	10		
20	9th	6,000	57	29	11	3	
21	5th	8,500	63	29	7	1	
22	3d	8,200	51	24	19	6	

accompanied by a rise in the pulse rate to 120 or 130, but considered throughout the disease the pulse was a slow one like that of typhoid fever.

The *heart* showed no variations from the normal except in one case. A soft blowing systolic murmur was audible in this case following the crisis. The point of greatest intensity shifted and the quality of the murmur changed from day to day, and these peculiarities, in conjunction with the temperature curve of sepsis, led to a clinical diagnosis of acute endocarditis, which was confirmed subsequently at necropsy.

Digestive System—Anorexia developed early and persisted throughout the febrile period. It was profound in 30 per cent of the cases. The tongue was flabby, moist and swollen early in the disease, coated along the dorsum and clean at the tip and edges. Later

the tongue became dry and the coating darker and thicker. In the severer cases the lips were parched and fissured and sordes collected on the teeth. Nausea and vomiting occurred at the onset in six cases and during the course of the disease in four cases. In one case it was so persistent that the patient could retain nothing but champagne. Intestinal symptoms were conspicuous by their absence. Meteorism, abdominal pain, tenderness or diarrhea were not encountered once in twenty-three cases. The spleen could be palpated below the costal margin in twelve of the twenty-three cases. The enlargement occurred early, being elicited on the second or third day in six cases, on the fourth day in three, while in the remaining three cases it was demonstrable on the fifth, sixth and seventh days, respectively. The liver was palpable in but one case. Scleral jaundice was observed once.

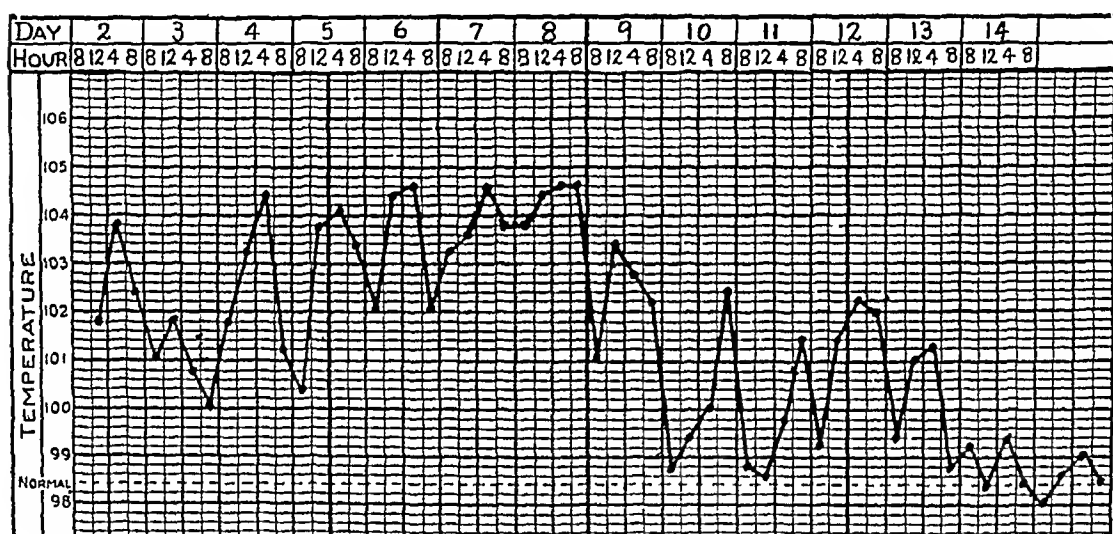


Chart 1—Temperature chart in a severe case of typhus

Respiratory System—Epistaxis, so constant a feature in typhoid fever, occurred but twice in our series, once on the second day while the patient's face was almost purple from congestion, and in the second case on the ninth day, preceding the crisis. Irritative cough without physical signs to account for it was observed twice. Hypostatic congestion and edema of the lungs occurred as terminal features in one case. Pleurisy with effusion complicated one case.

Nervous System—Signs referable to the nervous system were common, and it appeared to stand the brunt of the infection. Constant harrassing headache constituted the dominant symptom to the patient's mind. It developed at the onset and usually persisted until the sixth day. It was frontal as a rule, but in some cases the head ached "all over" and in one case the pain was occipital. Tremor of the tongue was observed in nineteen cases, of the lips in fifteen cases, of the hands in fourteen, and six of the patients had tremulous speech. The trem-

ors were coarse and of the intention variety, becoming apparent on voluntary efforts such as protruding the tongue, talking, or buttoning the pajama shirt. In two cases tremor of the tongue was incoördinate in character, and the patients instinctively held the organ protruded with the aid of the teeth. Delirium occurred in two cases. It was low and muttering without noisy manifestations in both instances and in both cases it preceded the crisis. Coma vigil, carphologia, subsultus tendinum and relaxation of the sphincters occurred in one case. Visual hallucinations were recorded once. Insomnia, ascribable to the constant harassing headache, occurred in 26 per cent of our cases. Tinnitus aurium and partial deafness in both ears, transitory in character, followed the crisis in one case.

Urinary System—Retention of urine occurred rather persistently in one case, necessitating frequent catheterization. Polyuria was an almost invariable concomitant of the crisis. The urine was high colored and showed the usual febrile changes—concentration, high specific gravity, marked acidity and increase of solids. Albumin, sugar or casts were not demonstrated. The kidneys showed moderate parenchymatous degeneration at necropsy in one case.

Relapse—A relapse, intercurrent in character, occurred in one case. During the initial febrile movement the temperature became subnormal on the morning of the sixth day, and then oscillated between 97 or 98 and 100 F until the fifteenth day, the evening temperature never reaching normal. From the ninth to the fifteenth day the patient was up and about and desired to return to duty. On the sixteenth day he had a distinct chill, and the temperature suddenly rose from 97.2 to 102 F. Blood was negative for malaria, and careful physical examination failed to reveal any cause for the chill and fever. The fever of the relapse continued for twelve days. Constipation, backache, profound anorexia and nervousness accompanied the relapse. No eruption was observed.

MORTALITY

One death, due to acute ulcerative endocarditis following the crisis, occurred in the series of twenty-three cases, establishing a death rate of 4.34 per cent.

DIAGNOSIS

Sporadic cases of the disease observed here would have undoubtedly been diagnosed as cases of fever of undetermined type, as the teaching has been that typhus fever is a disease of cold or temperate climates, and one would think of the possibility of its existence in the Philippines only after having thoroughly eliminated every other possibility. Having established the identity of the primary cases, the diagnosis of subsequent cases was not difficult.

Clinically, the striking features of the disease were intense headache, conjunctival injection, tremor of tongue, hands and lips, and the history of an initial chill followed by an abrupt rise of temperature. An eruption appearing usually on the fifth day, in conjunction with the foregoing features, clinched the diagnosis. The so-called tache cérébrale was a constant feature and, although it may be elicited occasionally in other diseases, its constancy was an aid to diagnosis in our cases. Negative findings of importance were the absence of plasmodia in the blood and the failure to cultivate any organism from the blood by ordinary methods. A history of living in, or having visited, an endemic center was also of value.

Isolated cases of this disease might be confounded with measles, relapsing fever, cerebrospinal meningitis, uremia, pneumonia, or in the

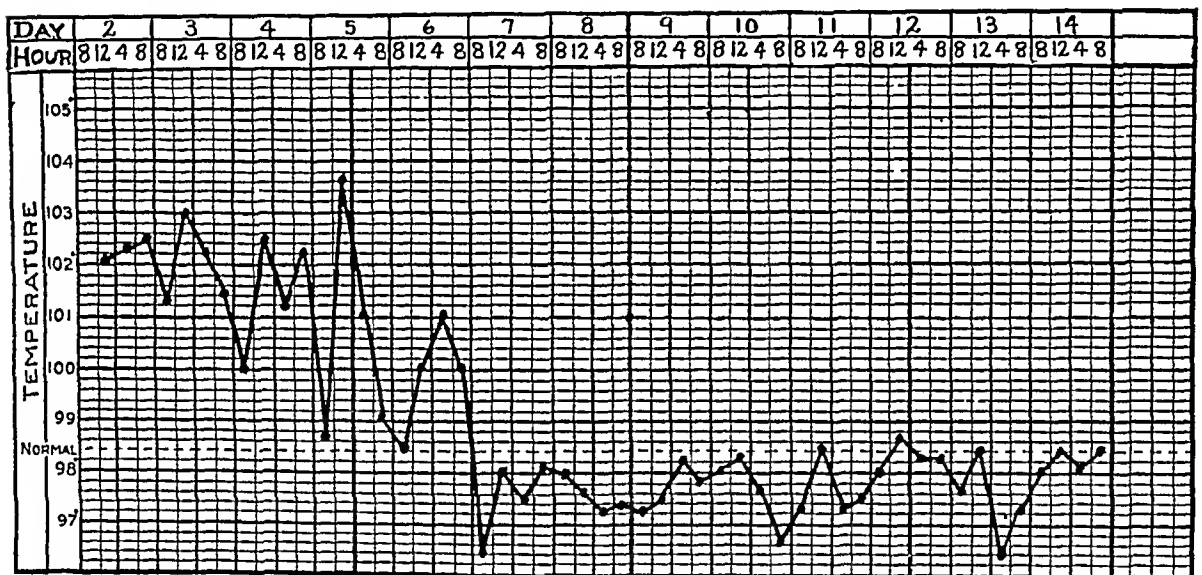


Chart 2—Temperature chart in a mild case of typhus

preeruptive stage, with smallpox. In reviewing the endemic, however, these diseases may be dismissed at a glance. The disease bore certain resemblances to other diseases which require more careful differentiation, and these will be considered seriatim.

Typhoid fever is characterized by a gradual onset, the course of the fever is longer, defervescence is by lysis and convalescence is not rapid. Abdominal symptoms, absent in our cases, constitute a prominent feature of typhoid. The eruption of typhoid appears on the seventh or eighth day and consists of rose-colored spots. In our cases the eruption could be looked for on the fifth day, and the spots were darker in color and more profuse than those of typhoid. The typhoid bacillus may be isolated from blood cultures in 90 per cent of typhoid cases during the first week of the disease, while, in our experience, blood cultures were uniformly negative. An additional factor is that

our patients, with the exception of five civilians, had been immunized against typhoid by protective inoculation, and, although an occasional case of typhoid may be expected among those who have been immunized, the possibility of numerous cases occurring is extremely remote

Dengue, as remarked by Manson, "bursts upon a place" and the majority of those in the community are stricken with certainty and rapidity following the introduction of the first case. The disease is characterized by a two-phased fever, marked arthritic and muscular pains, constant leukopenia and a tendency to slow convalescence during which rheumatic stiffness and twinges in the muscles and joints are common. In contrast to this picture, our cases showed no tendency toward pandemicity, the temperature curve was that of continued fever, pains in the muscles and joints were not harassing, the leukocyte counts frequently showed slight or moderate leukocytosis, and convalescence was rapid and uninterrupted.

Influenza, another pandemic disease, may be dismissed because of the endemic character of our cases and the absence of catarrhal symptoms.

Malaria may be eliminated in view of the uniform absence of plasmodia in the blood of our cases, the character of the temperature curve, and the negative results of therapeutic tests with quinin.

EXPERIMENTAL TYPHUS IN ANIMALS

Three monkeys and ten guinea-pigs were inoculated with blood from various cases of the series—mild and severe—during the febrile period.

The blood was drawn directly from the median basilic, or median cephalic vein and, without being defibrinated, diluted with saline solution or otherwise treated, was injected intraperitoneally at the bedside. The amount of blood injected was uniformly 3 c c, and the intraperitoneal route was the one invariably chosen.

Brief protocols of the experiments follow.

MONKEY 1 (Mike)—Male, nativity, Samar, P I, species undetermined but one that is common in the Philippines, weight, 5½ pounds. Inoculated intraperitoneally with 3 c c, of blood from Case 14. The patient was in the third day of the disease at the time the blood was taken and was extremely ill. The eruption was just appearing. The monkey was in robust health. His normal temperature, taken morning and evening for three days prior to inoculation, ranged between 101 and 102.2 F. Following inoculation there was a gradual daily fall in temperature for six days, but the animal was responsive, appetite was normal and there was no evidence of illness until the tenth day. In other words, the incubatory period of nine days was silent. On the tenth day following inoculation, the animal sat huddled up, his fur was ruffled, and, in contrast to his previous behavior, he lay perfectly quiet while the temperature was taken. As the attendant expressed it, he was "droopy." The tem-

perature began to rise, reaching its fastigium—103.4 F—seven days after the onset of illness. On the following day, the eighth day of illness, the temperature dropped 4 degrees by crisis. The animal was weak and unresponsive for several days following the crisis, and emaciation, which became evident at that time, persisted for several weeks. No eruption was noted.

MONKEY 2 (Pat)—Male, nativity, Samar, P I, same species as Monkey 1, weight 9½ pounds. Inoculated intraperitoneally with 3 cc of blood from Patient 15, at the time in the fifth day of his illness, with eruption out all over the body and symptoms marked. The course of the disease in this animal was essentially the same as in Monkey 1. The period of incubation was approximately eight days, during which the animal remained well. During the febrile period of seven days signs of illness—huddled posture, ruffled fur, anorexia and lassitude—were evident. The temperature reached its fastigium—103.6 F—within thirty-six hours of the onset, remained elevated four days and declined by rapid lysis, the entire febrile period occupying about seven days. The normal temperature of this animal lay between 101 and 102 F during the three days preceding inoculation. Emaciation became evident after the fever declined. No eruption was detected.

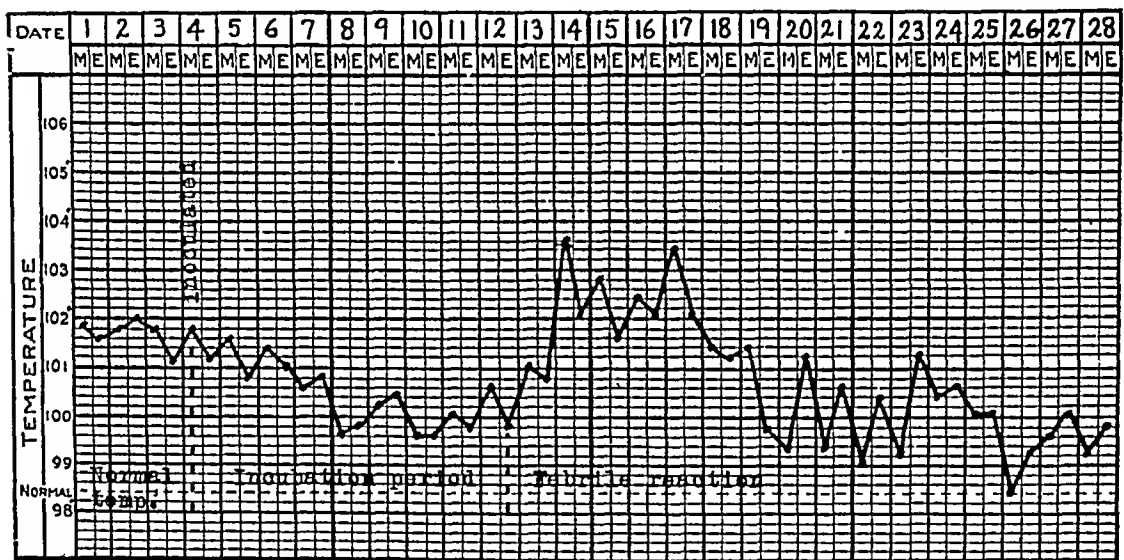


Chart 3—Febrile reaction in Monkey 2, following intraperitoneal inoculation with blood from a typhus case

MONKEY 3 (Moro)—Male, nativity, Mindanao, P I, species common in Mindanao, but different from that of Monkeys 1 and 2, weight 6 pounds. Inoculated intraperitoneally with 3 cc of blood from Case 17 on the seventh day of illness. Patient was not severely ill. In this animal no palpable evidences of illness were detected. During the second week following inoculation there was questionable fever, but the reaction was too doubtful to classify as positive.

GUINEA-FIG 1—Inoculated intraperitoneally with 3 cc of blood from Case 8. Blood taken on the seventh day while the disease was at its height. Reaction doubtful.

GUINEA-FIG 2—Inoculated in same manner as previous animals with blood from Case 9, the one case of the series which terminated in death. Reaction questionable.

GUINEA-FIG 3—Inoculated in the usual manner with blood taken from Case 10, one of the mildest clinically of the series. Blood taken on the sixth day of the disease. In this animal there was a well-marked incubatory period of ten days during which the animal showed nothing abnormal. On the eleventh

day the temperature began to rise, reaching 103.6 F on the seventeenth day. During the night the temperature dropped sharply to 100 F, and the animal lay huddled in a corner, obviously ill. Respirations were rapid and shallow and the animal refused to eat. The temperature again rose sharply to 103.8 F and then declined, the animal dying the following afternoon, eighteen days after inoculation and about eight days after the onset of illness. Necropsy showed congestion and edema of the lungs. No other gross changes were demonstrated.

GUINEA-PIG 4—Inoculated in the routine manner from Case 11 during the third day of the disease. Temperature rose sharply to 104 F in twenty-four hours. It declined gradually to 101 F and, running a continuous course between 101 and 102 F for two weeks, suddenly dropped to 99 F, the point at which it had registered when the animal was inoculated. In the absence of a definite incubation period in this case, the reaction was classified as doubtful.

GUINEA-PIG 5—This animal received intraperitoneally 3 c.c. of blood from Case 12, taken on the fourth day of the disease. The temperature curve was readily divided into three parts—incubation, febrile period and postfebrile period—at a glance. The period of incubation was ten days. The fever reached its fastigium on the second day following the onset, ran a continuous course for seven days, and defervescence occurred by rapid lysis in thirty-six hours. The febrile period occupied approximately ten days.

GUINEA-PIG 6—Inoculated in the usual manner with blood from Case 13. Blood taken on the fourth day. Except for an abrupt rise in temperature to 103 F on the sixth day following inoculation, which may have heralded an abortive attack, nothing significant was noted, and the result was classified as questionable.

GUINEA-PIG 7—Inoculated from Case 14, together with Monkey 1, during the third day of the disease. Result negative.

GUINEA-PIG 8—Received intraperitoneally 3 c.c. of blood from Case 15 during the fifth day of the disease. The temperature of this animal had been taken morning and evening for five days preceding inoculation, and the incubation period and febrile movement that followed were clearly defined. The period of incubation occupied nine days, and the fever, abrupt in onset and ending by crisis, lasted five days.

GUINEA-PIG 9—This animal was inoculated intraperitoneally with 3 c.c. of blood from Case 16. Blood taken on the fifth (?) day of the disease. Temperature ranged between 99 and 101.4 F, and this being within the limits of normal in the guinea-pig, it was believed that the result was negative. On the twenty-sixth day after inoculation, however, the animal died. Necropsy showed the entire thoracic cavity filled with fluid blood and recent clots. The pericardium was intact and contained no blood. The right lung was atelectatic and the lymph nodes at the root of the lung were enormously enlarged, pale, and breaking down. Source of intrathoracic hemorrhage, although searched for diligently, could not be found. Hemorrhage probably occurred from erosion of a pulmonary vessel embedded in the mass of glands at the root of the lung. The liver and kidneys showed slight parenchymatous degeneration. Smears from the lymph nodes stained with Wright's stain, and by approved methods for the demonstration of tubercle bacilli, were negative for bacteria. Cultures remained sterile for ten days.

GUINEA-PIG 10—Received intraperitoneally 3 c.c. of blood taken from Case 17 on the seventh day of the disease. The animal died suddenly ten days after inoculation. On opening the chest at necropsy the pericardium was distended with blood, on removal of which rupture of the right ventricular wall was revealed. The myocardium showed moderate parenchymatous change. There was intense pulmonary congestion.

Summarizing the results of the experimental inoculations recorded above, it will be noted that a definite febrile reaction occurred in 53·8 per cent of the inoculated animals, while in the remaining 46·2 per cent the reaction was negative or too questionable to be classified.

The incubation period varied from eight to ten days, during which the animal remained well. This was followed by an abrupt or gradual rise of temperature, the fastigium being reached on the second to the seventh day. The febrile period occupied from five to ten days, and the temperature defervesced by crisis or rapid lysis through forty-eight hours. In addition to fever, two monkeys and one guinea-pig exhibited loss of appetite, ruffling of the hair, huddled posture and "droopiness." An eruption was not observed. Emaciation was evident in two monkeys for a considerable time after recovery. Death terminated the infection in three instances.

In comparing these results with those of others, notably Nicolle and Conseil,⁹ Anderson and Goldberger,¹⁰ and Ricketts and Wilder,¹¹ it is believed that our attempts to infect monkeys and guinea-pigs with the virus of endemic typhus fever were successful.

Anderson and Goldberger¹⁰ outline the typhus reaction observed in monkeys as follows:

Following an inoculation with virulent material the monkey continues for a period varying from five to twenty-four days as if nothing had happened.

In about 90 per cent of the cases the incubation period varies between six and ten days.

At the end of this period the temperature of the susceptible animal rises fairly rapidly as a rule, sometimes gradually or at times very abruptly. The fever reaches its fastigium in thirty-six to forty-eight or seventy-two hours, it then continues for a variable period of one or two to five or more days, then defervesces. The defervescence, like the invasion, is variable, although usually gradual, it is frequently rapid or even critical. In brief, the course of the fever in the monkey is essentially like that of the fever in man.

The fever may be accompanied by loss of appetite, thirst, a ruffling of the hair, and a drooping posture, very commonly, however, even with a well-defined febrile reaction, the animal except for some slight listlessness shows hardly any outward manifestations. In other words, the fever is the only definite index of a reaction. In about 76 per cent of the cases the fever varies in duration between six and ten days.

At the termination of the fever there is almost always manifest some degree of emaciation.

They state, further, that in their experience a very large proportion—22·5 per cent—of monkeys possess at least a transitory immunity to

9 Nicolle and Conseil. *Ann de l'Inst Pasteur*, April and May, 1912, abstr., *Progr Med*, March, 1913, p. 225.

10 Anderson and Goldberger. *Natural and Induced Immunity to Typhus Fever*, Tr. Fifteenth Internat Cong Hyg and Demography, II, Part 1, p. 17.

11 Ricketts and Wilder. *The Transmission of the Typhus Fever of Mexico (Tabardillo) by Means of the Louse (Pediculus Vestimenti)*, Jour Am Med Assn, 1910, LV, 1304.

the injection of virulent typhus blood from infected monkeys, and that inoculation of virulent blood from man, whether New York or Mexico City cases, was successful in only a few cases. This explains the apparently negative result following inoculation in our Monkey 3 (Moro).

In 1912, Nicolle and Conseil⁹ demonstrated that the guinea-pig is susceptible to infection with typhus when inoculated intraperitoneally with from 2 to 4 c c of blood from man or monkeys. The incubatory period varied from seven to sixteen days. This was followed by fever lasting from four to eleven days, with an average of about a week. Toward the end of the febrile period there was a small loss in weight. They conclude that unless the temperature be taken, the infection may pass unobserved, in other words, the temperature curve is the only index of infection.

Results similar to these have since been reported by Anderson¹² and by workers¹³ in the Research Laboratories of the New York Department of Health.

EPIDEMIOLOGY

Climate—Camp Keithley is on the north shore of Lake Lanao, Mindanao, P. I. It is 8 degrees north of the equator. Reference to the Medical History of the Post shows that the annual rainfall during the year July 1, 1908, to June 30, 1909, was 98.46 inches. The highest monthly rainfall was 22.14 inches and the lowest 3.22 inches. There is practically no dry season. According to the geographic definition, the post is in the heart of the tropical zone, but owing to the altitude and the proximity of a large body of water fed by cold mountain streams, the climate is temperate rather than tropical. Palms, the presence of which constitutes "the truest expression of the tropical climate," do not flourish. The heat is never sufficient to cause one the slightest discomfort while, on the other hand, blankets at night are not only desirable but necessary for comfort.

Typhus fever is preeminently a disease of cold and temperate climates. As Castellani and Chalmers¹⁴ point out, the disease appears in the tropics at high altitudes, principally, and it quickly dies out with the onset of hot weather. We are told that the typhus of Mexico (tabardillo) occurs constantly on the great Mexican plateau, while in the coast towns the disease is rarely encountered.

¹² Anderson, John F. The Problem of Typhus in the United States, Jour. Am. Med. Assn., 1913, ix, 1846.

¹³ Nicoll, Krumweide, and others. Collected Studies, Bureau of Laboratories, N. Y. Dept. of Health, 1912-1913, vii, 132.

¹⁴ Castellani and Chalmers. Manual of Tropical Medicine, Ed. 2, New York, William Wood & Co., 1913, p. 1094.

In view of the recently acquired knowledge that the disease is transmitted by the louse, it is difficult to connect its occurrence in the tropics with the peculiar climatic conditions incident to altitude. The louse is omnipresent—in the lowlands as well as in the hills. The explanation may lie in the fact that the coast natives, unaccustomed to the chilly night air of the highlands, hermetically seal their quarters and huddle together for greater warmth, thus not only creating filth, overcrowding and bad ventilation—predisposing factors which lower their resistance to infection—but, by more intimate contact, augmenting the passage of the transmitting agent from one to the other.

Season—The twenty-three cases studied during the present endemic were evenly distributed, practically, over the months of September, October and November, the latter part, roughly, of the so-called rainy season.

Sex—Males constituted 82.62 per cent of the patients, while 17.38 per cent were females.

Age—Practically all the cases occurred in the third decade of life. Not a single case was seen in a child, and this is remarkable because of the large number of children exposed in the endemic foci from which the majority of the cases came. It is in harmony, however, with the experiences of Nicolle and Conseil¹⁵ at Tunis. They found that nursing infants are immune to infection, and that older children may have the disease in so mild a form that it may escape detection. This emphasizes the importance of recognizing mild cases of typhus in children which, unrecognized, may act as missing epidemiologic links and cause the continuance of an outbreak.

Endemic Foci—Two distinct foci from which the disease disseminated were detected in connection with this endemic. The primary focus was a corral that had been converted into living quarters for families of enlisted men of the twenty-fifth and twenty-eighth companies, Philippine Scouts. The building is 170 feet long and 36 feet wide and is divided into twenty-six stalls, 14 feet deep by 10 feet wide, with two small rooms at each end. The building was converted into living quarters by closing in the stalls with sheets of iron roofing and building floors of scrap lumber. No provisions for lighting or ventilation existed, and the quarters were damp, dark and poorly ventilated. Twenty-seven compartments in this building were occupied by 103 persons—thirty men, thirty-one women and forty-two children—living in filth and squalor. Superficial examination showed the heads of many of these people infected with pediculi. That many of the

¹⁵ Nicolle and Conseil. *Gaz. d. hôp.*, April 9, 1911, p. 609, abstr. *Progr. Med.*, March 1913, p. 228.

women and children were ill-nourished needs no emphasis when it is remembered that they were dependent for their subsistence on native soldiers whose monthly wage is \$7 50

Filth, overcrowding, poor ventilation, ill nourishment and vermin combined to form exact conditions for the spread of typhus fever

Two of the occupants gave a clear-cut history of recent attacks of fever, which undoubtedly was typhus in view of the information subsequently received from a typhus patient infected by these people. Three other women looked ill, and one of these may have been convalescing from typhus, as her husband was subsequently under observation with well-marked symptoms

The second endemic focus was the so-called *barrio* of Bungalow just beyond the limits of the military reservation and under the jurisdiction of the civil authorities of Dansalan. This *barrio* is composed of native shacks, tenanted by scout soldiers and their families

The first three cases encountered were in married men who, when not on duty, slept at the corral. The fourth case was in a recruit who had not been away from the reservation and as he gave a history of having visited the corral, and other possibilities were not elicited, the assumption was that infection had been contracted on one of these visits. The fifth, sixth and seventh cases were, like the first three, in married men who lived at the corral. The information elicited from the eighth patient, an officer's servant, stamped the corral as the undoubted source of infection. She stated that she frequently visited the wife of a corporal of the Twenty-Eighth Company, who lived at the corral, and that she invariably visited there on Saturdays and Sundays. September 21 and 22 she slept at the corral and stated that the corporal's wife was ill with *calentura* (fever) at that time, that the woman was taken ill, September 8, and that her illness lasted two weeks. The corporal, who nursed his wife, was taken ill September 22, and was ill ten days. The officer's servant became ill October 5, fourteen days after sleeping at the corral.

Patients 10, 11 and 14 lived at the corral and were infected there unquestionably. The source of infection in Cases 13 and 15 was not ascertained with certainty. They had visited the corral eleven and twenty-four days prior to the onset of illness, respectively, and although an incubation period of twenty-four days is unusual, it is possible that both were infected at that time. Patient 16 had a family quarantined at the corral, and it is possible that he—as occurred in two other instances—had broken quarantine and was infected during a clandestine visit.

Patient 18 was admitted to the hospital on the fifth day of the disease. She lived at Bungalow and was the first case from that endemic

focus. She had formerly lived at the corral but denied having visited there for several months. Patient 19 was a recruit who probably contracted the disease while visiting a brother living in the house in Bungalow from which Case 18 was taken. Patient 23, the brother whom Patient 19 had visited, was admitted subsequently. Patients 20 and 21 were both married men who lived at Bungalow, and it seems reasonable to connect them with the other cases of infection there.

The source of infection in Cases 12, 17 and 22 could not be ascertained.

Origin of the Endemic—Efforts to trace this endemic to a single original case have been unsuccessful. The clinical records of the last thousand cases admitted to the hospital at Camp Keithley have been reviewed, and from them six cases of fever have been culled which resemble cases of typhus observed during this endemic. The first of these cases was admitted May 28, 1913, another occurred in June, a third in July, and two more in December. The sixth case was admitted in February, 1914. Diagnoses of malaria were made in four of the cases, one was diagnosed intestinal autointoxication, and the sixth was diagnosed as paratyphoid fever. The malarias exhibited courses of fever similar to that of typhus, plasmodia were not demonstrated and quinin in large doses did not influence the temperature curve. The clinical records show no other instances of paratyphoid infection, and, as the diagnosis of paratyphoid fever in the sixth case was made in the absence of confirmatory evidence from the laboratory, it is believed that it should be viewed with considerable mental reservation. The diagnosis "intestinal autointoxication" is very frequently open to suspicion.

If we accept these instances of probable cases of typhus fever, the history of the disease extends back to May, 1913, at least.

My predecessor, Captain Pipes, of the Medical Corps, informed me that he had encountered cases of fever in Moros identical with the first case of typhus observed here, and was very anxious that the identity of the disease, the nature of which had not been determined at that time, be established. Information from various sources is in accord with Captain Pipes' statement. Mr. Moore, at the time acting provincial fiscal, recently related the occurrence of a fever similar to ours among the Cotabato Moros, and Captain Fletcher, P. S., states that the Moros of Romain Valley, in this province (Lanao), who live in old overcrowded cottas, report many cases of a fever that is attended with high mortality.

It is probable that typhus has existed in endemic form in Mindanao for an indefinite period, being looked on by the native, as all fevers are, as a form of malaria.

Whether the disease was originally introduced by religious pilgrims returning from Mecca, where typhus occurs in epidemic form, or whether it may have followed the lines of commercial intercourse from Japan are matters of conjecture

Transmission —Experimental transmission of the disease to monkeys by means of the louse, along the lines pursued by Anderson and Goldberger,¹⁶ Ricketts and Wilder,¹¹ and others was not attempted. In the absence of proper facilities for safeguarding such experiments, there would have been constant danger of infected lice escaping, and the attempts would have been foolhardy.

The epidemiologic data point, however, to the louse as the probable transmitting agent, and the evidence is strengthened by the fact that preventive measures aimed at ridding patients and contacts of lice broke up two proved endemic centers, and resulted in the disappearance of the disease.

A striking characteristic of this endemic, in connection with the theory of louse transmission, which is in accord with the experiences of those who have followed epidemics of typhus in Tunis, Belfast and Mexico City, is that the disease has been connected invariably, with squalid environment. Our cases did not come from the families of officers, from the quarters of American noncommissioned officers, or from company barracks, although these places are not immune to the visitations of measles, malaria or dengue when such diseases are prevalent. On the other hand, the disease occurred constantly among those having more or less intimate daily contact with native women. The explanation may be that the louse occurs in the former places only under most exceptional circumstances, while it is as indigenous to the native woman as the flea is to the dog.

Entomologists state that the body louse (*Pediculus vestimenti*) is not found in the Philippines.¹⁷ This is interesting, as it is the louse that is commonly believed to be the transmitting agent in typhus fever. However, Anderson and Goldberger¹⁶ have recently demonstrated that the head louse (*Pediculus capitis*) is also capable of transmitting the disease, and the fact that the body louse is not found here does not weaken my conviction that the louse was the means of transmission during the recent endemic.

Flying insects, such as the mosquito or fly, may safely be ruled out as possible transmitting agents, as the disease remained restricted to

16 Anderson and Goldberger. The Transmission of Typhus Fever, with Especial Reference to Transmission by the Head-Louse (*Pediculus Capitis*), Pub. Health Rep., March 1, 1912.

17 Insects and Disease, Health Bull. No. 11, Bureau of Health, P. I., 1913, p. 15. Ann. Rep. Bureau of Health, P. I., June 30, 1912, p. 95.

areas beyond which it would have been carried with certainty by such intermediaries. No evidence was adduced that would inculcate the bedbug or flea. Transmission by food or drink is too remote a possibility to consider. That aerial transmission or fomites played no part in the dissemination of the disease seems evident in view of the fact that neither attendants nor other patients became infected at the hospital, where contact with fomites from typhus patients was more or less unavoidable for a period of three months.

I believe that consideration of the data outlined above justifies the opinion that the disease described is typhus fever. Further investigation along the line of experimental transmission by means of the louse would be interesting, and it is believed that the identity of this fever and Brill's disease might be established by cross-immunity tests with animals inoculated in the United States.

Anomalous fevers are common in the Philippines, and it is unfortunate that research workers confine their activities so largely to Manila, while interesting fields for investigation in the provinces are neglected. Field work similar to that prosecuted by officers of the Public Health Service in the southern United States would illuminate the medical geography of the Philippine Islands.

SOME CONSIDERATIONS IN THE STUDY OF INFANTILE TETANY, WITH REPORT OF A CASE^{*}

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For years it has been known that the effect of an inorganic salt on the irritability of nerve and muscle tissue is influenced by the presence of another salt in the solution. Ringer¹ was the first to discover that the twitchings of a frog's muscle produced by immersing it in an isotonic solution of pure sodium chlorid, were abolished by the addition of a small amount of calcium. J. Loeb² pointed out that the toxicity of a sodium chlorid solution was not due solely to the absence of calcium, but also to the presence of the sodium ion, since distilled water had no such toxic action. He also suggested that irritability depends on various ions, especially the metallic ions, Na, Ca, K and Mg, existing in definite proportion in the tissue.

But since the effect of an alteration in these proportions varies widely in different species of animals, no general law embracing the action of these ions has yet been formulated, and for particular tissues and species, the result of any salt disturbance must be determined.

In spite of this, clinical investigation in tetany has been largely directed towards a study of calcium metabolism, and the discussion of its pathogenesis has largely centered around the calcium content of the tissues. The clinical results, however, have not been satisfactory or in any way conclusive. The almost constant co-existence of rickets with infantile tetany has presented further difficulty in the interpretation of the results, and changes in the calcium balance may be secondary to the amount of calcium deposited in the bones and not due to any change in the content of the nerve substance or body tissues in general. In experimental tetany produced by parathyroidectomy, an increased loss of calcium occurs, and administration of calcium reduces, temporarily although never permanently, both the electrical irritability and the severity of the convulsions. Other salts, however, such as magnesium and strontium also produce this effect. Mac-

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1 Ringer Jour Physiol, 1886, vii, 291

2 Loeb, J. Am Jour Physiol, 1910, iii, 383, Jour Biol Chem, 1905, i, 427

Callum, Lambert, and Vogel³ were able to produce extreme nerve hyperexcitability by perfusion of an organ with blood the calcium of which had been removed by dialysis

Clinical results have been somewhat less constant. As a general rule, during the onset of the eclampsia, a decrease in the calcium retention occurs, and the reverse sets in during convalescence. The symptoms of the disease also can often be partially checked by the injection of a calcium salt. But this loss of calcium is not always found (Stoeltzner⁴) and administering calcium either with the food or by injection is frequently without result (Haskins and Gerstenberger⁵)

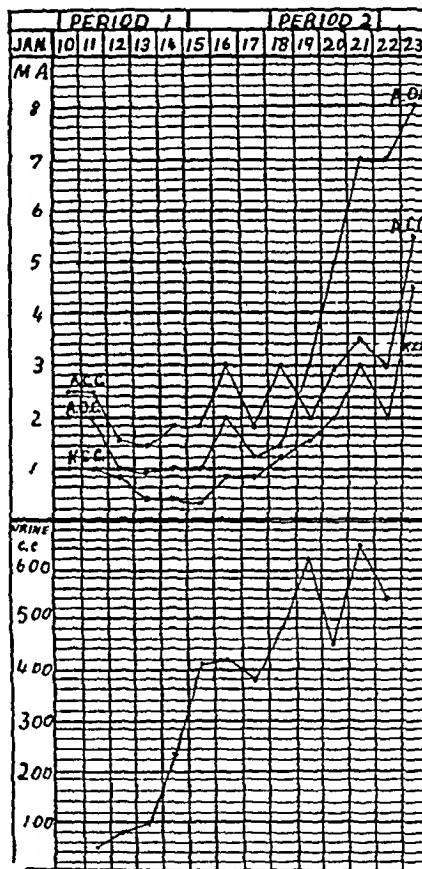


Chart showing variations in the electrical irritability and in the volume of the urine during periods of observation

More recently, attention has been given to the effect of the other kations. It has long been the experience of pediatricians that cow's milk and particularly whey will aggravate infantile tetany, yet the organic constituents of milk (casein, fat, or sugar) have by themselves no such untoward effect. On the other hand, the inorganic salts of milk do affect the irritability, and this can frequently be demonstrated clinically. Calcium and magnesium, when administered

3 MacCallum, Lambert and Vogel Jour Exper Med, 1914, xx, 149

4 Stoeltzner Jahrb f Kinderh, 1906, lxi, 661

5 Haskins and Gerstenberger Jour Exper Med, 1911, xiii, 314

subcutaneously, bring about, as a rule, a temporary fall in the irritability and a quiescence of the tetany. This is especially the case with magnesium, which, following the recommendations of Behrend,⁶ is frequently used with considerable success as a means of combating the convulsions. The salts of the alkalies act in the opposite direction. Grulee,⁷ on adding sodium or potassium chlorid to the food of spasmophilic children, obtained an increase in the irritability. Lust⁸ confirmed these observations and obtained most striking results with potassium. He also records a case of tetany in which each exacerbation was accompanied by a temporary increase of weight, due to a retention of salts and fluid, the so-called metabolism edema.

These facts suggest that the effect of inorganic salts on nervous tissue is not so much determined by the concentration of any one ion, but rather by their relationship to each other, and that it is some disturbance of the usual equilibrium that upsets the normal reaction of the nerve cell. A few years ago, Aschenheim⁹ made estimations of the brain tissues in spasmophilia and found that, while the calcium and magnesium were most frequently decreased, sometimes they were unchanged and the sodium and potassium increased, the only constant factor being an increase in the quotient $\frac{Na + K}{Ca + Mg}$. He therefore concludes that the hyperexcitability is due to an increase in this factor. Further support of this hypothesis has been furnished by the researches of Reiss.¹⁰

Clinically very little work has been done to determine under what conditions these salt disturbances in tetany are induced and what the underlying factors are in their production. In recording the following case, a preliminary report of an investigation being carried on in Toronto along this line is presented.

CASE REPORT

History—G. McK., male, aged 13½ months, was admitted Jan. 7, 1915, to the Infants' Department at the Sick Children's Hospital. Breast fed for nine months, supplemented with Allenbury's food for part of time, and then with arrowroot biscuit. Diarrhea at 3 months of age, lasting one month. Lately fed on Horlick's malted milk. Dec. 15, 1914, the first attack of tetany occurred, lasting about half a minute, described as a stiffening of the body accompanied by the spasm of the hand and foot characteristic of tetany. Before this, he had been constipated for some time and, until time of admission, bowel movements were produced only by enemata, the stools being small and hard. December 24 a more severe and prolonged attack took place, during which the child

6 Behrend *Monatschr f Kinderh*, 1913, xii, 269

7 Grulee *Jour Am Med Assn*, 1912, lix, 938

8 Lust *Munchen med Wchnschr*, 1913, lx, 1482

9 Aschenheim *Monatschr f Kinderh*, 1910, ix, 366

10 Reiss *Ztschr f Kinderh*, 1911, iii, 1

became cyanosed and seemed to struggle for breath. Similar convulsions then occurred at frequent intervals. During this period he became cross and irritable and cried almost constantly.

Examination—Examination on admission showed a child under weight for age, with a fair amount of subcutaneous tissue of diminished turgor. Feet and hands in typical position of carpopedal spasm. Spleen slightly enlarged. Slight craniotabes and enlargement of the epiphyses of long bones (evidence of rickets). Cried, while being examined, continuously, with occasional crowing inspiration. Chvostek's and Trousseau's symptoms present. Muscle jerks easily elicited. Odor of acetone in breath.

Treatment—He was offered a milk mixture made up of evaporated milk, ounces 10, barley flour, ounces $1\frac{1}{2}$, lactose, ounce 1, water, up to ounces 40. Eight ounces were given every four hours, five times a day. A good deal was at first refused. Cod liver oil (20 min) and phosphorus (gr $1/300$) three times a day. Jan 10, 1915, he was put in a metabolism bed and observed up to January 15. During this period of five days he was obstinately constipated, having three dark, yellow, foul-smelling stools produced in each case by half an ounce of castor oil. He became more restless and irritable. The laryngospasm increased. The electrical irritability on January 10 was K C C 1, A O C 2, A C C 25, and on January 15 K C C 04, A O C 10, A C C 18. The weight increased from 13 pounds 9 ounces to 14 pounds 3 ounces, and, during this period, very little urine was passed, although the amount increased towards the end of the period. Signs unchanged, no convulsions.

January 16, 1 gm of urea was added to the food daily to stimulate the diuresis which had already begun. From January 18 to January 22 observations were again made. During this period a striking change occurred. The child took more food and became less restless, the bowels moved without the use of castor oil, and the stools became lighter in color and less offensive. The urine flow was much freer, the electrical irritability decreased from K C C 12, A C C 3, A O C 14 on January 18 to K C C 2, A C C 3, A O C 7 on January 22. An increase of four ounces in weight occurred. The carpopedal spasm disappeared. Trousseau's sign could not be obtained, and a slight twitch only could be seen in eliciting Chvostek's symptom.

Subsequently the child continued to improve and went on to good recovery.

During the periods of observation the patient was placed in a metabolism bed, the amount of food taken each day measured, and a proportionate part used for analysis. The urine and feces were collected separately. The specimens were dried and ashed by Bunge's method. Sodium and potassium were weighed as chlorids, and separated by platinic chlorid. The calcium and magnesium were weighed as calcium oxid and magnesium pyrophosphate, following McCrudden's¹¹ method. The electrical irritability was determined by placing the anode or kathode over the head of the fibula and the neutral pole over the abdomen. The minimum current which would produce a contraction of the peronei was estimated in milliamperes.

The case presented an opportunity for observation during a period of intensification of the symptoms and during a period of improvement. Variations in the electrical irritability and in the urine secretion are shown in the accompanying chart.

¹¹ McCrudden Jour Biol Chem, 1910, vii, 83

The daily average estimations made of Period 1 are shown in Table 1

TABLE 1—DAILY AVERAGE METABOLISM ESTIMATIONS IN PERIOD 1

	Amount gm or c c	Sodium Oxid	Potassium Oxid	Calcium Oxid	Magnesium Oxid
Milk		0 1754	0 5460	0 4686	0 0324
Feces	14 6	0 0194	0 0387	0 0779	0 0076
Urine	176 0	0 0129	0 0609	0 0017	0 0216
Total loss		0 0323	0 0996	0 0796	0 0292
Balance		+0 1431	+0 4464	+0 3890	+0 0032
Balance in per cent of intake		81 6	81 7	83 1	9 8

A marked retention of all the salts has occurred, which would go hand in hand with the retention of fluid and the gain in weight of this period. But this retention has not been uniform, and its outstanding irregularities are, first, the large amount of potassium (0 4464 K_2O), second, the small amount of magnesium (0 0032 MgO)

The relative proportion of alkali to alkali earth $\frac{Na + K}{Ca + Mg}$ is 1 501

The results from Period 2 were as shown in Table 2

TABLE 2—DAILY AVERAGE METABOLISM ESTIMATIONS IN PERIOD 2

	Amount gm or c c	Sodium Oxid	Potassium Oxid	Calcium Oxid	Magnesium Oxid
Milk		0 2706	0 8331	0 6948	0 1136
Feces	51 7	0 0099	0 0770	0 2478	0 0279
Urine	585 0	0 1157	0 5359	0 0081	0 0149
Total loss		0 1256	0 6129	0 2559	0 0428
Balance		+0 1450	+0 2202	+0 4389	+0 0706
Balance in per cent of intake		53 2	26 4	63 2	62 1

Here the proportions are reversed. The retained potassium has been cut in half, a daily balance of 0 4464 being reduced to 0 2202, and, while the former represents 81 per cent of the intake, the latter is only 26 4 per cent of the potassium in the food. The sodium retention has increased 0 002 gm, but the balance in terms of the intake has decreased from 81 6 per cent to 53 2 per cent. The calcium balance has decreased from 83 1 per cent to 63 2 per cent of the intake, and its absolute value has increased 0 050 gm only, but the balance is now nearly twice that of any of the other metals. The magnesium balance has increased almost twenty-fold, i e., from 0 0032 to 0 0706, or, in

per cent of the intake, 98 per cent to 62.1. In the second period the quotient $\frac{\text{Na} + \text{K}}{\text{Ca} + \text{Mg}}$ is reduced to 0.717.

Examination of the calcium estimations by themselves would not lead one to believe that calcium changes could be held responsible for the development of tetany, and the figures demonstrate that actual loss of calcium is by no means essential for its production. In fact, the irritability has increased over a period of five days during which 0.3896 gm of CaO were being daily retained in the tissues. Examined in connection with the other metals, the relative increase in the calcium retention during the second period becomes quite evident, being greater than the weight of the three other metals combined.

During this period of improvement, the body has been excreting the alkalies of the food and it is of special clinical interest to observe that nearly all of this excretion was performed by the kidney. This excretion occurred simultaneously with an increased flow of urine, whereas in the first period, during which the alkalies were retained, the kidneys were remarkably inactive. At the same time the restoration of the normal salt equilibrium took place along with an improvement in the gastro-intestinal system. The stools became less offensive and the bowels less constipated, the appetite improved and more food was taken. The association of fluid retention and gastro-intestinal disturbance, observed in the first period, is seen not infrequently in children, and the former seems to depend directly on the digestive disturbance since observation has shown that it can be controlled by dietetic changes, and disappears as the digestion improves. Carbohydrates and the salts of sodium and potassium are especially liable to induce these fluid changes and may well be reduced when there is any reason to believe that fluids are being retained. Taking away part of the whey from the food, as is sometimes done in the treatment of tetany, is a means of lowering the sodium and potassium intake, the calcium remains in the curd.

The importance of the kidney in regulating the salt equilibrium is evident from the figures given, and, when the urine is small in amount, the kidney may be stimulated by means of an organic diuretic—such as urea—1 gm of which was given daily with the food.

The high magnesium balance is noteworthy in view of the specific action of magnesium upon nerve tissue. Its narcotic effect led Behrend⁶ to use it in checking the symptoms of tetany. He found, however, that the magnesium, when given subcutaneously, is excreted again within twenty-four hours, and that injections must be repeated daily. A similar experience has been had in rickets, in which calcium, if injected, is not retained, yet, as convalescence begins, this loss stops and the tissues regain the power of retaining calcium. So in tetany,

with improvement, the body begins to re-establish the normal salt relationship, and the ability of the tissues to hold magnesium may be an evidence of a subsidence of the disease

To sum up briefly Clinical observation would not warrant the conclusion that calcium changes alone account for the nerve irritability in tetany, but would seem to support the hypothesis that the tetany results from a disturbance of the concentration equilibrium of the salts

Such salt changes are probably associated with gastro-intestinal disturbances and decreased activity of the kidney, and, as improvement in the function of these two systems occurs, restoration of the normal salt equilibrium ensues Treatment, accordingly, from these indications should aim at restoring a normal digestion and increasing the activity of the kidney

A SIMPLE METHOD FOR DETERMINING VARIATIONS IN THE HYDROGEN-ION CONCENTRATION OF THE BLOOD *

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AND

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Human blood, as it exists in the body, is faintly alkaline in reaction that is, it has a hydrogen-ion concentration only slightly less than that of pure water, and this degree of alkalinity tends to be maintained even when considerable quantities of acid are produced within the body, or are introduced from without

To a relative increase in the acid content of the body, the term "acidosis" is applied. Acidosis, conceivably, may be brought about in other ways than those just mentioned—for example, by decreased excretion of acid or by loss of bases from the body. The condition has been recognized in a variety of ways, such as increase in the ammonia coefficient of the urine, decrease of carbon dioxide tension in the alveolar air, the finding of abnormal acids in the blood and urine, by increased alkali tolerance and by diminished titratable alkalinity of the blood serum, by changes in the hemoglobin dissociation curve and by actual determination of the hydrogen-ion concentration of the blood. Production of ammonia, lowering of carbon dioxide tension in the alveolar air and in the blood, and excretion of acids are all part of the compensatory mechanism of the body, and it is only when this mechanism becomes overtaxed that appreciable changes in the hydrogen-ion concentration of the blood occur. The blood itself, owing chiefly to the "buffer" action of the carbonates of the plasma and phosphates of the corpuscles, can take up considerable amounts of acid or alkali without much change in its reaction. It is principally due to the work of L J Henderson¹ and his collaborators that we have a clear conception of the mode of action of these "buffers." An appreciable change in the hydrogen ion concentration of the blood indicates a failure of the protective mechanism and the presence of a significant acidosis. Herein lies the peculiar value of a determination of the hydrogen-ion concentration of the blood.

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1 For a full discussion, see Henderson, L J. *Ergebn d Physiol*, 1909, *viii*, 298

A brief word of explanation may be given for those unaccustomed to the physicochemical methods of expressing the reaction of a solution. A solution is acid when it contains an excess of hydrogen over hydroxyl ions, neutral when hydrogen and hydroxyl ions are in equal numbers, and alkaline when hydroxyl ions predominate. An acid of "normal" strength contains, in one liter, a gram of hydrogen capable of forming hydrogen ions,² and its strength may be expressed as 1 N. Diluting such a solution ten times, we would have 1/10 N or a solution containing 1/10 gram of actual or potential hydrogen ions to the liter. Continuing the process of dilution until 1/10,000,000 normal acid is obtained, we would have in such a solution 1/10,000,000 gram of hydrogen ions. Pure water, however, dissociates to form hydrogen and hydroxyl ions, and at 20 C contains approximately 1/10,000,000 gram of hydrogen ions to the liter and an equivalent amount of hydroxyl ions (that is, 17 gm). That is to say, pure water, our standard of neutrality, is 1/10,000,000 N acid and also 1/10,000,000 N alkaline. To avoid writing large figures it is customary to use the logarithmic notation and to express 1/10,000,000 N as 10^{-7} N or, more conveniently, as suggested by Sorensen,³ to drop the 10 and minus sign and say⁴ pH7. If we have less than 1/10,000,000 gram of hydrogen ions to the liter, the solution is less acid than water, that is, it is alkaline—so, pH8 means actually 1/1,000,000 N alkali. The higher the exponent the more alkaline, or what is saying the same thing, the less acid is the solution.

To sum up

$$\text{pH1} = \text{N/10 acid}$$

$$\begin{aligned}\text{pH6} &= \text{N/1,000,000 acid} \\ \text{pH7} &= \text{NEUTRALITY} \\ \text{pH8} &= \text{N/1,000,000 alkali}\end{aligned}$$

$$\text{pH14} = \text{N/10 alkali}$$

The reaction of the blood serum varies approximately between pH7 and pH8, the neutral point, pH7 being reached only in severe uncompensated acidosis, and a reaction of pH8 being attained perhaps only after administration of alkalis.

The measurement of the pH of the blood as compared with that of inorganic solutions presents many difficulties. The standard gas chain electrometric method has been applied to the blood by a number of investigators. A full review of the literature up to 1910 is to be found in an article by Botazzi.⁵ More recent determinations have been made

2 For the sake of simplicity we will consider here only a "strong" acid and assume it to be completely ionized in dilute solution.

3 Sorensen. *Ergebn d. Physiol*, 1912, xii, 401.

4 CH7 and $[\text{H}^+] = 7$ are synonymous expressions. Intermediate values, as, for example between pH7 and pH8, are commonly expressed in one of two ways, as 0.25×10^{-7} or $\text{pH} = 7.6$. The latter method is used in this paper. The conversion of one expression into the other is simple. For example, $\log 0.25 = -0.602$, then $0.25 \times 10^{-7} = 10^{-0.602} \times 10^{-7} = 10^{-7.602}$ or $\text{pH} = 7.602$.

5 Botazzi. *Der Harn sowie die ubrigen Ausscheidungen und Korperflussigkeiten*, edited by C. Neuberg, Berlin, 1911.

by Hasselbalch and Lundsgaard,⁶ Peters,⁷ Peabody⁸ and Milroy⁹ The results have not been altogether uniform, and the accuracy of the method as applied to blood is questionable on account of the necessary reduction of the hemoglobin, and the influence of the protein substances present

The fact that the gas chain method of determining the pH of the blood requires a delicate and expensive piece of physicochemical apparatus as well as considerable technical training has been standing in the way of clinical investigations of acidosis directly from the side of the blood, and has led to the very valuable but indirect methods of approach, such as those utilized in the studies of Sellards,¹⁰ Palmer and Henderson¹¹ and Adler and Blake¹²

PRINCIPLE OF THE METHOD

Heretofore the indicator method has not proved of great value in the studies of hydrogen-ion concentration of the blood, although the reaction of inorganic solutions may be determined quite accurately by this means¹³ Different indicators show their color changes at varying degrees of hydrogen-ion concentration, for example, the color of methyl orange changes from pink to yellow as the pH of its solution changes from 3 to 5 At intermediate points, various colors may be obtained and a certain color indicates a definite pH Similarly, phenolphthalein changes from colorless to pink between pH8 and pH10 and can be used for the measurement of H-ion concentrations between these two points In carrying out the indicator method, it is necessary to have a series of standard solutions of known pH and an indicator exhibiting easily distinguishable color changes at hydrogen-ion concentrations approximating that of the solution under consideration It is then simply necessary to add equal amounts of indicator to the standard solutions and to the solution being tested and to determine which of the colors in the standard solutions most closely matches that of the unknown solution

6 Hasselbalch and Lundsgaard *Biochem Ztschr*, 1912, xxxviii, 77 Lundsgaard *Ibid*, 1912, xli, 247

7 Peters *Physiol Soc Prac*, January, 1914

8 Peabody, F W *Studies on Acidosis and Dyspnea in Renal and Cardiac Disease THE ARCHIVES INT MED*, 1914, xiv, 236

9 Milroy *Quart Jour Exper Physiol*, 1914, viii, 141

10 Sellards *Johns Hopkins Hosp Bull*, 1912, xxiii, 289, *ibid*, 1914, xxv, 101

11 Palmer, W W, and Henderson, L J *Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, THE ARCHIVES INT MED*, 1913, xii, 153

12 Adler, H M, and Blake, Gerald *The Retention of Alkali by the Kidney with Special Reference to Acidosis, THE ARCHIVES INT MED*, 1911, vii, 479

13 For a full description of the application of indicators to this purpose, see Sorensen *Ergebn d Physiol*, 1912, xii, 393

This method has been successfully used on the urine by Henderson¹⁴ and by Walpole¹⁵. As proteins interfere with the colors of many indicators, and as both blood and serum possess color, it has been impossible to apply the method directly to the blood¹⁶.

It seemed probable that the indicator method might be utilized for blood, provided coloring matters and proteins could be excluded by means of dialysis¹⁷. If blood is dropped into collodion sacs and dialyzed for five minutes, the dialysate is free from proteins and coloring matter, but contains salts, and is well adapted to the use of indicators.

Since phenolsulphonephthalein exhibits definite variations in quality of color, with very minute differences in hydrogen-ion concentration between pH 6.4 and 8.4, it was adopted as the indicator in this method.

PREPARATION OF STANDARD COLORS

Standard phosphate mixtures are prepared according to Sorensen's¹⁸ directions as follows:

1/15 mol acid or primary potassium phosphate 9.078 grams of the pure recrystallized salt (KH_2PO_4) is dissolved in freshly distilled water and made up to 1 liter.

1/15 mol alkaline or secondary sodium phosphate The pure recrystallized salt ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) is exposed to the air for from ten days to two weeks, protected from dust. Ten molecules of water of crystallization are given off and a salt of the formula $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ is obtained, 11.876 grams of this is dissolved in freshly distilled water and made up to 1 liter. The solution should give a deep rose red color with phenolphthalein. If only a faint pink color is obtained, the salt is not sufficiently pure.

The solutions are mixed in the proportions indicated below to obtain the desired pH.

pH	64	66	68	70	71	72	73	74	75	76	77	78	80	82	84							
Primary Potas Phos , c c	73	63	51	37	32	27	23	19	15	8	13	2	11	0	8	8	5	6	3	2	2	0
Secondary Sodium Phos , c c	27	37	49	63	68	73	77	81	84	2	8	8	89	0	91	2	94	4	96	8	98	0

Three c c of each of the solutions are placed in suitable small test tubes (100 × 10 mm, inside measurement). Five drops of an aqueous

14 Henderson *Biochem Ztschr*, 1910, xxiv, 40

15 Walpole *Biochem Jour*, 1910, v, 207

16 Sorensen (*Biochem Ztschr*, 1909, xxii, 238) has applied the indicator method to the filtrate obtained after precipitating blood or serum by boiling with three volumes of dilute hydrochloric acid. Adler (*Am Jour Physiol*, 1907, xix, 1) has tested the reaction of the serum with paper dyed pink with rosolic acid. The objections to these methods are obvious.

17 Preliminary experiments showed that it was impossible, by the indicator method, to obtain concordant results on dilutions of serum.

18 Sorensen *Biochem Ztschr*, 1909, xxii, 352

0.01 per cent solution of phenolsulphonephthalein are added to each tube. The tops are sealed off. The series of colors, representing different concentrations of hydrogen ions, constitutes the standards for comparison of color in carrying out the determination.¹⁹

PREPARATION OF SACS

One ounce of celloidin (Anthony's negative cotton)²⁰ is dissolved in 500 c.c. of a mixture of equal quantities of ether and ethyl alcohol. The solid swells up and dissolves with occasional gentle shakings, in forty-eight hours. As a small amount of brown sediment separates out at first, the solution should stand for at least three or four days, after which the clear supernatant solution is ready for use.²¹ A small test tube (120 by 9 mm inside measurement) is filled with this mixture, inverted, and half the contents poured out. The tube is then righted, and the collodion allowed to fill the lower half again. A second time it is inverted and rotated on its vertical axis, the collodion being drained off. Care must be taken to rotate the tube, in order to secure a uniform thickness throughout. The tube is clamped in the inverted position and allowed to stand for ten minutes, until the odor of ether finally disappears. It is filled five or six times with cold water, or it is allowed to soak five minutes in cold water. A knife blade is run around the upper rim, so as to loosen the sac from the rim of the test tube, and a few cubic centimeters of water are run down between the sac and the glass of the tube. By gentle pulling the tube is extracted, after which it is preserved by complete immersion in water.²²

THE SALT SOLUTION USED IN THE METHOD

The blood or serum is dialyzed against an 0.8 per cent sodium chlorid solution.

Before applying the test, it is necessary to ascertain that the solution is free from acids other than carbonic. To determine this, a few cubic centimeters of the salt solution are placed in a Jena test tube and one or two drops of the indicator added, whereupon a yellow color appears. On boiling, carbon dioxide is expelled, and the solution loses its lemon color and takes on a slightly brownish tint. In the absence of this change, other acids are present, and the salt solution is therefore not suitable.²³ If, on the other hand, on adding the indicator, pink at once appears, the solution is alkaline and hence cannot be used.

TECHNIC OF METHOD

The technic can be carried out on either serum, plasma, whole or defibrinated blood. The work must be done in a room free from fumes of acids or ammonia.

19 The colors may fade slightly in a month's time, but may still be used for comparison if less indicator is added to the "unknown" solution, as the color quality remains the same.

20 Obtained from the Ansco Co., Binghamton, N. Y. This contains 30 per cent of water and must be rinsed with absolute alcohol before being dissolved for use.

21 Better sacs are obtained from solutions that have been allowed to "age" in well-stoppered bottles for from two to three weeks.

22 Sacs that have dried become brittle and impervious.

23 It is advisable to keep the salt solution in a Jena glass flask and to protect it from acids in the air by means of a soda lime tube.

One to three c c of clear serum²⁴ or of blood is run, by means of a blunt pointed pipet, into a dialyzing sac which has been washed inside and outside with salt solution and which has been tested for leaks by filling with the salt solution²⁵ The sac is lowered into a small test tube (100 by 10 mm, inside measurements) containing 3 c c of the salt solution, until the fluid on the outside of the sac is as high as on the inside From five to ten minutes are allowed for dialysis²⁶ The collodion sac is removed and 5 drops of the indicator are thoroughly mixed with the dialysate The tube is then compared with the series of standards until the corresponding color is found, which indicates the hydrogen-ion concentration present in the dialysate

These tests have been carried out with 3 c c of blood or serum The same results are obtained with 1 c c of blood or serum on the inside of the sac, and with this amount it is immaterial whether there is 1 or 3 c c of salt solution on the outside

COMPARISON OF TUBES WITH STANDARDS

For this, a good light (natural or artificial) and a white background are requisites Readings must be made immediately The tube matching²⁷ most closely is selected and also the tubes on either side of it These are critically inspected against a white background Changing the order of the tubes often makes differences more apparent²⁸

CONTROLS OF THE METHOD

Repeated duplicate determinations on the same samples of blood and of serum have convinced us that the limits of error are very slight for example, the serum from a case of mild acidosis (using quantities of serum varying from 1 to 3 c c and dialyzing for from five to fifteen minutes) gave the following series of readings 7.55, 7.55, 7.55, 7.55, 7.6, 7.55, 7.55, 7.55, 7.55, 7.55 The oxalated whole blood from the same case gave the following readings under similar conditions 7.25, 7.25, 7.25, 7.25, 7.2, 7.25, 7.25, 7.3, 7.25, 7.25, 7.25, 7.25, 7.25.

24 Hemolysis tends to increase the acidity and must be avoided

25 A sac may be used more than once for serum, provided it is thoroughly washed

26 The alkalinity of the dialysate increases rapidly during the first five minutes There is no appreciable change during the next ten minutes Proteins may make their appearance in the dialysate in from ten to twenty minutes

27 It must be borne in mind that one is here matching the quality of color and not intensity as in ordinary colorimetry

28 A color falling between two of the standards may be read, by interpolation, to another decimal place No effort was ever made to read closer than 0.05 Duplicate determinations should be made in all cases when sufficient material is available

In order to test out the effect of the variations in the sacs used, a number of determinations were made on the same sample of serum with the following results ordinary thin sac, 77, thick sac, 77, opaque, irregular sac, 77, ordinary thin sac, 7.65, very thick sac, 77. A series of six normal serums were run through, 3 cc and 1 cc portions being used for dialysis. In every instance identical readings were obtained.

APPLICATION OF THE METHOD

Having thus assured ourselves of the accuracy of the method, a series of bloods from normal and pathologic cases were studied, with the following results.

1 *Normal individuals*, twenty-five cases (a) Serum, Twenty-four of the twenty-five cases read between 7.6 and 7.8. In one instance, 7.9 is recorded.

pH	Cases
7.6	4
7.65	1
7.7	5
7.75	5
7.8	9
7.9	1

(b) Whole blood (oxalated²⁹); nineteen determinations. These all read between 7.4 and 7.6.

pH	Cases
7.4	3
7.45	2
7.5	4
7.55	5
7.6	5

The slightly greater acidity of whole blood as compared with serum has been recognized by almost all investigators in this field, and appears to be due to the fact that hemoglobin, and especially oxyhemoglobin, behaves as a weak acid.

(c) Defibrinated blood. Early in the course of the work, defibrinated blood was run in parallel series with serum and oxalated whole blood. It was found that in general, the results tended to correspond to those obtained with the whole blood, but the range of variation was rather wide from 7.4 to 7.8. No additional information was obtained, and the defibrination merely served to complicate the procedure. Hence it was decided to abandon the use of defibrinated blood in the subsequent course of the investigation.

2 *Miscellaneous medical cases*. In order to determine whether the hydrogen-ion concentration of the blood varies from the normal in disease, a rather large variety of conditions was studied. Sixty-three

²⁹ The blood was collected in tubes containing a little dry powdered sodium oxalate (free from carbonate).

determinations were made in 52 cases, comprising the following conditions nephritis (acute and chronic), 12 cases, diabetes mellitus, 8 cases, myocardial insufficiency, 5 cases, syphilis, 4 cases, chronic arthritis, 3 cases, pernicious anemia, 2 cases, neuroses, 3 cases, and 1 case each of pyelitis, empyema, carcinoma of neck, hemorrhoids, typhoid fever, pneumonia, meningococcus meningitis, tuberculous meningitis, cholelithiasis (jaundice), pulmonary edema, cerebral hemorrhage (coma), tuberculous pleurisy, foot and mouth disease, angio-neurotic edema and brain tumor

The results were as follows

(a) Serum, sixty-three determinations Sixty of the sixty-three determinations read between 7.6 and 7.8

pH	Cases
7.6	14
7.65	4
7.7	19
7.75	1
7.8	22

The three exceptions not coming within these limits were

(1) An instance of traumatic neurosis with a reading of 7.9 (2) A febrile typhoid with a reading of 8.0 (3) A case of chronic nephritis with hematemesis from an acute gastric ulcer, whose serum after the transfusion of 850 c c of blood, by the syringe method, gave a reading of 7.95

(b) Whole blood (oxalated), thirty-three determinations, of which thirty-one read between 7.4 and 7.6

pH	Cases
7.4	1
7.45	2
7.5	10
7.55	8
7.6	10

The two exceptions were instances of pernicious anemia. The first case, immediately following transfusion, gave a reading of 7.7 on the whole blood, this being identical with that on the serum. It is of interest to note that before transfusion the readings on the serum and whole blood were also the same, that is, 7.6. The second case gave a reading of 7.65 in the whole blood, this again being identical with that on the serum.

3 *Acidosis* From the preceding paragraphs it is evident that the hydrogen-ion concentration of the whole blood or serum, normally and in a great variety of disease conditions, is not subject to great variations. A small series of cases with clinical or laboratory evidence of acidosis (or both) has been studied, the results appearing in Table 1. Fifteen determinations were made in eight cases³⁰

30 Detailed clinical histories are appended at the end of this paper

TABLE 1—ACIDOSIS (EIGHT CASES, FIFTEEN DETERMINATIONS)

Case No	Date	H-Ion Concentration		Diagnosis and Remarks
		Serum	Whole Blood (Oxal)	
1	12/26/14	.	71	Congenital cystic kidneys, adherent pericardium, myocardial insufficiency, hydrothorax, ascites, uremia, 'phthalein, trace in two hours, CO ₂ tension of alveolar air, 19.5 mm Hg
	1/2/15	74		Dull, drowsy, 'phthalein, still only a trace in two hours
2	12/3/14	72		Acute and chronic nephritis, hypertension, uremia, 'phthalein, trace in two hours, Sellards' test, complete decolorization on evaporation
3	1/13/15	7.55		Eclampsia,* mild toxemia
4	1/25/15	75	73	Eclampsia,* severe toxemia NH ₃ nitrogen in urine, 18 per cent
	1/29/15	78	75	Thirty-six hours after labor, alkali therapy, doing well
5	1/18/15	72		Sarcoma of kidney and antrum, acidosis, sudden onset of acidosis with "air hunger", Sellards' test, complete decolorization on evaporation, acetone and diacetic acid in urine
	1/19/15	74.5		After large doses of alkali, better, Sellards' test, faint pink color before complete evaporation
	1/28/15	78		More alkali, no dyspnea
	2/18/15	73		Respirations again deep and noisy, acetone in urine
6	1/22/15	75		Recurrent vomiting, no food retained for three days, acetone and diacetic acid in urine
7	1/22/15	74		Alimentary intoxication
	1/22/15	7.55		After alkali therapy, death next day
8	1/8/15	74		Acute and chronic nephritis, myocardial insufficiency (slight), anasarca, dyspnea, 'phthalein, 55 per cent in two hours, acetone in urine
	1/20/15	76	75	Much improved, CO ₂ tension of alveolar air, 40.1 mm Hg

* We are indebted to Dr J Whitridge Williams for permission to study these cases occurring in his service

CHANGES IN THE HYDROGEN-ION CONCENTRATION OF THE BLOOD
IN EXPERIMENTAL CONDITIONS

An effort has been made to see if similar changes in the pH of the blood and serum can be demonstrated in experimental acidosis in dogs. Animals were injected intravenously with dilute hydrochloric acid. Protocols of two experiments are given in Tables 2 and 3.

TABLE 2—PROTOCOL OF EXPERIMENT 1—INTRAVENOUS INJECTION OF N/3 HYDROCHLORIC ACID INTO A DOG* (FEMALE, WEIGHT 7.3 KG)

Time p m	Amt of HCl Injected c c	H-Ion Concentration			Remarks
		Serum	Whole Blood (Oval)	Blood Drawn Directly Into Sac	
3 43	50	7 75	7 6	7 55	Breathing normally
3 44-3 49		7 65	7 4	7 45	
4 00		7 7	7 45		
4 14	40				No essential change in condition
4 17-4 23		7 6	7 5	7 4	
4 26	30				Toward end of injection, respirations slow and deep, 14 per minute
4 50-4 56					
5 00	40	7 65	7 55	7 5	Marked "air hunger" respirations, 11 per minute, pulse, 31 to 1/4, regular
5 03					Respirations still slow but shallower, animal in fairly good condition
5 21-5 30					At 5 26 respirations 11 per minute
5 45		7 45	7 45	7 4	Restless, struggling
5 50					Off table, no "air hunger", lying down in no apparent discomfort, recovered

* Injections made in part into jugular, in part into leg vein. Blood for examination withdrawn either from jugular or leg vein on opposite side. HCl made up in 0.8 per cent salt solution.

GENERAL DISCUSSION

In order to determine the actual hydrogen ion concentration of the blood as it exists in the body, it is necessary that measurements be made at body temperature and under the carbon dioxide tension existing in the vessels as shown by analysis of the alveolar air. Most of the published results do not fulfil these two requirements and therefore do not give the reaction, as Lundsgaard³¹ expresses it, *strictissimo sensu*.

In a study of acidosis, however, these considerations are of academic rather than of clinical importance, since we are concerned with variations in the pH rather than with its actual value

The more recent electrometric measurements have been carried out at the carbon dioxide tension existing in the alveolar air and in most cases at room temperature (18 C) So long as the measurements are made at a constant tension of carbon dioxide and at a constant temperature, the results are of value for comparative purposes

TABLE 3—PROTOCOL OF EXPERIMENT 2—INTRAVENOUS INJECTION OF N/2 HYDROCHLORIC ACID INTO A DOG (FEMALE, WEIGHT 7 KG)

Time	Amt of HCl Injected	H-Ion Concentration		Remarks
		Serum	Whole Blood (Oxal)	
3 21 3 28 3 36	Injection begun	77	7 55	Serum light yellow, clear
3 50				Beginning to breathe deeply and slowly, heart's action very forceful, regular
3 56	90 c c have been injected	69	69	"Air hunger" marked, respirations, 28 per minute Heart's action forceful, regular, serum shows moderate amount of hemolysis
4 00 4 09	Injection ended, 105 c c have been injected	69	69	In extremis, gasping for breath, heart still beating strongly, serum shows marked hemolysis Ceased breathing, heart stopped beating, artificial respiration and intravenous injection of 5 per cent solution of sodium bicarbonate unavailing

In the method described in this paper, blood is exposed to the air so that the carbon dioxide tension is low, but apparently, fairly constant The objection might be made that the pH would depend on the amount of carbon dioxide which has escaped from the blood or serum The following experiments indicate, however, that the pH is not dependent, within reasonable limits, on the time elapsing between the taking of the blood and the determination of the pH, provided the

tube containing blood is kept stoppered and on ice, as will be seen from the following

	Serum	Oxalated Blood
Immediately	7.75	7.55
After 2½ hours	7.75	7.55
After 19 hours	7.75	7.55
After 24 hours	7.75	7.55

If, however, blood is drawn directly into a sac immersed in a tube of salt solution and the reading compared with that from the blood drawn and determined in the usual manner, slight variations are encountered (see Experiment 1)

By thoroughly shaking the blood or serum in the air, its alkalinity is increased. Therefore, shaking should, in general, be avoided, unless it is desired to determine the pH at a zero CO_2 tension. Such studies have been carried on by Dr. D. W. Wilson.

The influence of the temperature on the readings has been determined, and the results appear in the accompanying tabulation.

TABLE 4—VARIATIONS IN HYDROGEN ION CONCENTRATION DUE TO CHANGES IN TEMPERATURE

Temperature	A		B	
	Serum	Whole Blood (Oxal)	Serum	Whole Blood (Oxal)
20 C	7.75	7.55	7.75	7.45
30 C	7.85	7.5	7.8	7.4
37 C	7.9	7.65	7.9	7.45

This effect of temperature has been recognized by previous workers. It is evident that in order to obtain comparable results, temperature control is necessary. Our measurements have been made between 20 and 24 C.

The dialysate of the blood or serum is slightly more acid than the original material, if one can judge from experiments carried out with dilute sodium bicarbonate solutions containing carbon dioxide, and phosphates of approximately the pH and concentration of blood. That the variation is a constant one under the conditions of the method is shown by the close agreement of duplicate determinations, which has been referred to previously in this paper.

By a coincidence, the results obtained from the dialysate from the whole blood and from serum correspond very closely to those obtained directly by the electrical method when the latter measurement is made at 18 C and at a carbon dioxide tension of 40 mm Hg.

This agreement in results is probably due to the antagonistic character of the two main sources of error involved in the method of dialysis, namely, loss of carbon dioxide tending to give higher, that is, more alkaline readings, and disproportionate dialysis of acid and basic constituents yielding lower, that is, more acid readings. For clinical pur-

poses, particularly the study of acidosis, the method of dialysis is quite as applicable as the electrometric method, and yields results in general comparable with those of that method. It has the advantages of simplicity and rapidity.

CONCLUSIONS

1 The indicator method of determining H-ion concentration is made applicable to blood and serum by utilization of dialysis through a collodion membrane, which excludes the disturbing influences of color and of proteins. The method is simple, accurate, rapid and well adapted for clinical use.

2 The technic consists of dialyzing 3 c c of blood or serum at room temperature against 3 c c of 0.8 per cent salt solution for five minutes, adding an indicator and comparing with colored standard phosphate mixtures of known H-ion concentration.

3 Phenolsulphonephthalein is employed as the indicator in this method. It is found to exhibit easily distinguishable variations in quality of color, with minute differences in H-ion concentration between the limits pH 6.4 and pH 8.4.

4 Oxalated blood from normal individuals gives a dialysate with a pH varying from 7.4 to 7.6, while that of serum ranges from 7.6 to 7.8.

5 Variations from these figures toward the acid side were encountered only in conditions which clinically, and from the standpoint of the laboratory findings, evidenced an acidosis.

6 In a small series of clinical acidoses, the serums varied from 7.55 to 7.2 and the oxalated blood from 7.3 to 7.1. In experimental acidosis in dogs, a pH of 6.9 has been encountered in both serum and blood just before death.

REPORT OF CASES

CASE 1—H. S. (Medical No. 33,441), a white man, aged 43. Diagnosis: congenital cystic kidneys, adherent pericardium, myocardial insufficiency, edema of lungs, hydrothorax, and uremia. Admitted Dec. 12, 1914.

The patient had good general health until ten years ago. He had muscular rheumatism at eight. Eighteen years ago he had an attack of "acute Bright's disease," which confined him to bed for two weeks. Ten years ago, a lump was discovered in the left flank. Exploratory operation revealed congenital cystic kidneys and a few of the cysts in the right kidney were punctured. Five years later the left kidney also became palpable.

The present illness began five months before the patient's admission, with attacks of nocturnal dyspnea, which gradually became worse. Three weeks ago swelling of the legs appeared.

Examination showed an undernourished man, dyspneic and orthopneic. Signs of fluid were present in both pleural sacs, with bubbling râles over the lower lobes. There was marked cardiac enlargement and systolic retraction of inter-spaces lateral to apex. Broadbent's sign was present, also a protodiastolic gallop. There was a faint systolic blow at the apex, which was transmitted to the axilla. The pulmonic second sound was accentuated. The abdomen was

distended with fluid. A large mass covered with bosses was palpable in each flank. The liver was enlarged and tender. Edema of legs was noted.

Repeated phenolsulphonephthalein tests showed the excretion of only a trace in two hours.

The CO₂ tension of alveolar air was December 16, 23.3 mm Hg, December 18, 19.1 mm Hg.

The hydrogen-ion concentration of blood was December 26, whole blood, 7.1, January 2, serum, 7.4.

The nonprotein nitrogen of the blood was 118 mg per hundred cubic centimeters. The blood pressure ranged from 155 to 135 mm Hg systolic, 110 to 75, diastolic.

The urine was pale and clear with a specific gravity of 1.008 to 1.012. A trace of albumin and hyaline casts were observed. Acetone was present on several occasions. The patient was discharged Jan. 11, 1915, somewhat improved.

CASE 2—C O P (Medical No. 33,385), a white man aged 43. Diagnosis: arteriosclerosis, acute and chronic nephritis, hypertension and uremia. Admitted Dec. 1, 1914. The patient had syphilis twenty years ago and was treated by intermittent courses of mercury for four years. He had uncomplicated typhoid fever twenty-three years ago and from 1908 to 1912 drank heavily.

The present illness began two years ago with severe headaches, usually coming on in the early morning hours and becoming gradually more severe. Polyuria and nycturia soon followed. Three months ago he had an attack of sudden loss of consciousness with a generalized convulsion lasting five or six minutes, and followed by profuse vomiting. He was in bed for four days. There was no paralysis. Eight weeks before his admission blood was discovered in the urine. He was put to bed and has remained there since. Two months ago his eyesight began to fail, he is now unable to read.

Examination showed a fairly nourished man with pasty complexion and decidedly anemic appearance. The heart was moderately enlarged. There was a presystolic gallop with numerous extrasystoles. The second aortic sound was loud and ringing. The radials and brachials were diffusely thickened, the temporals tortuous and sclerosed. Advanced albuminuric retinitis was noted, with fresh hemorrhage in both eyes.

The blood count showed red blood cells, 3,520,000, white blood cells, 11,400, hemoglobin (Sahli) 65 per cent.

By the phenolsulphonephthalein test, excretion in two hours on numerous occasions ranged from a trace to 16 per cent. December 3, the patient was vomiting and belching at frequent intervals and was very drowsy.

Sellard's test on the blood serum showed complete decolorization on evaporation, no color on addition of water.

The hydrogen-ion concentration of the serum was 7.2. During the patient's stay in the hospital the blood pressure ranged from 208 to 174 systolic, 136 to 108 diastolic.

The urine in quantity was 1,025 to 5,025 cc in twenty-four hours, its specific gravity, 1.005 to 1.009. Smoky at first, it became clear with the polyuria, then bloody again. From 2 to 5 grams of albumin per liter were present. Hyaline, granular and blood casts were observed. The patient refused to remain for treatment and was discharged unimproved, Dec. 22, 1914.

CASE 3—F W (Obstetrical Service), a colored girl, aged 18, was admitted Jan. 8, 1915. Diagnosis: pre-eclamptic toxemia, postpartum eclampsia. The girl was nine months pregnant. On the day before admission, albumin and casts were found in the urine, and the patient was advised to enter the hospital. During the course of the next few days she complained of epigastric discomfort and frontal headaches of increasing severity. The systolic blood pressure was 190 mm Hg. On January 12, slight edema of the legs appeared.

On January 13, at 7.55 a.m., spontaneous labor occurred. Ten minutes after the birth of the child the patient had a typical eclamptic convulsion of moderate

severity lasting two minutes. The blood pressure (systolic) at this time was 150 mm Hg. There were two more convulsions that day. Following bleeding, purging and sweating, a normal convalescence ensued.

The hydrogen-ion concentration of the serum obtained at venesection was 7.55.

The nonprotein nitrogen in the blood was 42 mg per 100 cc.

January 24, the phenolsulphonephthalein test showed 55 per cent excretion in two hours.

The ammonia nitrogen in the urine

January 13 = 5 per cent

January 14 = 9 per cent

January 16 = 7 per cent

CASE 4—M K (Obstetrical Service), a white woman, aged 19, was admitted Jan 25, 1915. Diagnosis: eclampsia, spontaneous labor.

The patient was a strong, well-nourished primipara, nine months pregnant. The pregnancy had been uneventful until the morning of January 25, when, at 4 a. m., she began to have severe headache, nausea and vomiting. Shortly afterward she had one convulsion. When seen in the out-patient service she was conscious but drowsy. Blood pressure (systolic) was 150 mm Hg, the pulse 80 per minute. The urine showed 8 grams of albumin per liter.

She was admitted to the ward at 7 p. m., unconscious, exceedingly restless, and having typical, moderately severe eclamptic convulsions at intervals of three-quarters of an hour. The blood pressure (systolic) was 180 mm Hg. There was no dyspnea and very slight edema of lower legs. She had seven convulsions in all, the last occurring at 5 a. m. on the morning of January 26. Blood for hydrogen-ion determination, obtained after the third convulsion, gave a reading of 7.5 on the serum, 7.3 on the whole blood.

Following venesection, purgation and sweating, and the administration of 40 grams of sodium bicarbonate by stomach-tube the convulsions finally ceased and consciousness returned on the morning of January 26. On January 28 a dead child was born spontaneously. The puerperium was uneventful.

The ammonia nitrogen of the urine during the three days preceding delivery ranged from 18 to 10 per cent.

January 29, the hydrogen-ion concentration of blood was for the serum, 7.8, for the whole blood, 7.5.

CASE 5—L C (Harriet Lane Home No 6,538), a white boy, aged 3, was admitted Jan 13, 1915. Diagnosis: sarcoma of the kidney and antrum, acidosis.

The boy had been a normal, healthy child up to three months before admission, when, following a trauma to the face, a small, red swelling appeared on the left cheek, subsequently pushing through to the roof of the mouth. Though painless, this swelling had gradually grown larger.

Examination showed a well-developed, well-nourished child. There was a firm mass in the left cheek, apparently arising in the antrum, and pushing down the left side of the hard palate in the mouth. There was a nodular, firm mass, the size of a man's fist, in the right umbilical region.

January 16. Breathing was rapid and deep.

January 17. There was marked dyspnea, the respirations were 40 per minute.

January 18. Respirations unusually deep, with actual "air hunger." The urine contained acetone and diacetic acid.

Sellards' test showed colorless on complete evaporation. The hydrogen-ion concentration of the serum was 7.2. One hundred and seventy-five cc of a 5 per cent solution of sodium bicarbonate was given by the Murphy method. This was followed by 175 cc of a 4 per cent solution of sodium bicarbonate intravenously. After the first 50 cc, respirations became noticeably less labored, and shortly after the completion of the injection the child was quite comfortable. Small doses of bicarbonate were continued by mouth.

January 19 Sellards' test showed a faint pink color before complete evaporation

The hydrogen-ion concentration of the serum was 7.45 The child was breathing normally, though mentally rather dull

During the succeeding weeks several radium treatments were administered and it was believed that the abdominal mass had grown somewhat smaller

On February 18 the respirations became suddenly deep and noisy The child seemed drowsy The urine showed a trace of acetone, but no diacetic acid The patient was given alkali by mouth

The hydrogen-ion concentration of the serum was 7.3

On February 25 the patient was discharged Breathing again was normal though the general condition was failing

CASE 6—A McK (Harriet Lane Home), a white boy, aged 6, was admitted Jan 21, 1915 Diagnosis recurrent vomiting

The boy had been a normal child except that he had always had a "weak stomach" Three days before admission, following an indiscretion in diet, he complained of abdominal pain Next day he began to vomit and since then had not retained any food except a little orange juice He vomited without any apparent effort, and after vomiting seemed quite well

Examination showed a sparsely nourished child, apparently quite normal in all respects The urine contained acetone and diacetic acid The hydrogen-ion concentration of the blood serum was 7.5 Following a well-regulated dietary regimen, he rapidly improved and went home

CASE 7—V D (Harriet Lane Home No 6,628), a white girl, aged 2 months, was admitted Jan 22, 1915, died Jan 23, 1915 Diagnosis alimentary intoxication

The patient was a full-term, apparently healthy, child. Sixteen days before admission she began to vomit after every feeding and had frequent green stools The vomiting and diarrhea persisted up to the time she was brought to the hospital

Examination showed a small, moderately well-nourished baby, conscious and crying fretfully Slight cyanosis was present The respiratory rate was increased, the respirations being full and deep White blood cells, 22,170 The stool, large, green and watery, contained mucus and food residue

Sellards' test showed no color on evaporation or on addition of distilled water after evaporation

The hydrogen-ion concentration of the serum was 7.4

Intensive alkali therapy was given, both intravenously and subcutaneously The respirations improved a little, becoming shallower There was one slight convulsion and constant convulsive twitchings of the face and extremities

The hydrogen concentration of the serum after intravenous injections of sodium bicarbonate was 7.55

The respirations gradually became shallower and more infrequent and the baby died at 4.55 a m on January 23 There was complete anuria during the stay in the hospital Partial necropsy showed only enlargement of the mesenteric lymph nodes

CASE 8—M F (Medical Service), a white man, aged 20, was admitted Jan 7, 1915 Diagnosis acute and chronic nephritis, hypertension, and myocardial insufficiency

The patient had frequent sore throats Eighteen months ago he began to have morning headaches For three months, dyspnea on exertion was noted, becoming progressively more marked Six days before admission the feet and ankles began to swell, and the abdomen and face have since become edematous Anorexia, dizzy spells and epistaxis have occurred during the past week

Examination showed an overnourished young man, dyspneic, sallow and pale Marked oral sepsis was present, the tonsils were large and ragged Crepitant râles were heard at the left base The heart was markedly enlarged

There was a snapping aortic second sound The liver was enlarged and tender
Edema of feet and ankles was present There was a moderate secondary
anemia

The Wassermann test was negative

The phenolsulphonephthalein test showed 55 per cent of excretion in two
hours The hydrogen-ion concentration of the serum was 7.4 The nonprotein
nitrogen of the blood was 36 mg per 100 cc

January 20 The hydrogen-ion concentration of the serum was 7.6, whole
blood, 7.5 The CO₂ tension of alveolar air was 40.1 mm Hg

The urine in quantity was 1,500 to 2,000 cc in twenty-four hours The
specific gravity was 1.012 to 1.013 There were 15 to 275 grams of albumin
per liter On admission, red blood cells and acetone were observed, which subse-
quently disappeared Numerous granular casts were found

The blood pressure ranged from 170 to 130 mm Hg systolic, 110 to 65 dias-
tolic The patient is somewhat improved He is still in the hospital (April,
1915)

THE ROENTGENOLOGIC DETERMINATION OF GASTRIC MOTILITY

WITH A COMPARISON OF THE RESULTS OBTAINED IN A SERIES OF CASES
EXAMINED BOTH BY THE ROENTGEN RAY AND THE TEST-MEAL *

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The testing of gastric motility by roentgenologic methods has been of such striking and practical value that it seems worth while to report the results obtained in a considerable series of operated cases and to compare them with the findings gained by the test-meal and stomach tube. We have subjected approximately 10,000 patients to the Roentgen test, but have selected for tabular analysis and comparison those cases seen during the year 1914. In 1914, 4,118 patients were examined by the Roentgen ray for gastro-intestinal disease. Of this number 1,140 were operated on. In 950 of them a motor-meal test was also made by the gastro-enterologist and the tabulation is based on these 950 cases.

Before discussing the results it may be well to recall some of the elementary facts as to the physiology and pathology of the gastric motor function and recount some of the principal tests for disturbance in this respect.

It is almost superfluous to offer here a reminder of the magnificent work of William Beaumont, but so many of his conclusions remain uncontradicted to this day and the inspiration which he gave to accurate methods of observation have so strongly influenced our present conceptions that some of his findings with respect to motility require repetition. For example, his deduction¹ that "the time required for the digestion of food is various, depending upon the quantity and quality of the food, state of the stomach, etc., but that the time ordinarily required for the disposal of a moderate meal of the fibrous parts of meat, with bread, etc., is from three to three and a half hours." Further, he drew the "inference," as he expressed it, "that oily food is difficult of digestion" and that "water, ardent spirits and most other fluids are not affected by the gastric juice, but pass from the stomach as soon as they are received."

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¹ In the Life and Letters of Dr. William Beaumont, by Jesse S. Myer
St. Louis, C. V. Mosby Co., 1912, p. 201

Cannon² also, by his painstaking experiments on animals, has given us reliable data, among which may be summarized the following. The chyme does not pass through the pylorus at the approach of every peristaltic wave but emerges occasionally, at irregular intervals, of from ten to eighty seconds. Acid above opens and acid below closes the pylorus. Fats when given are almost invariably present in the stomach during seven hours observation. Water begins to enter the intestine almost as soon as it enters the stomach. Carbohydrates go through rapidly, proteins more slowly. When carbohydrates and proteins are given one after another the early rate of evacuation is largely the same as that of the first food given. Mixtures of carbohydrates and proteins have an emptying rate intermediate between that of carbohydrates and that of proteins. Fat retards the exit of either food-stuff from the stomach into the intestine. As to consistency of food materials, there is a marked retardation of the outgo of food from the stomach when hard particles are present. Considerable amounts of gas in the stomach retard the discharge of food. Rage, distress, anxiety, grief, anger and violent emotions have a depressive effect on gastric motor activities.

Besides the physiologic variations to which the gastric clearance time is subject, it may also undergo numerous pathologic alterations, in the direction either of an exaggeration or a diminution of motility. Thus we are familiar with the shortened gastric evacuation time of nonobstructive duodenal ulcer and of nonobstructive cancer of the stomach. On the other hand, we are equally familiar with the retarded emptying resulting from so-called atony of the stomach, hyperacidity, and reflex spasm of the pylorus, the latter either from an extrinsic cause, such as disease of the gallbladder, or from an intrinsic cause, such as gastric ulcer. Further, and more importantly, we are acquainted with the gastric retention produced by organic stenoses at or near the pylorus.

Now it would seem that by no simple test can sharp and constant lines of demarcation be drawn between hypermotility, normal motility and hypomotility. Nevertheless, extreme variations in either direction, more especially toward hypomotility, have high diagnostic significance, can be determined at least broadly, and efforts at such determination cannot safely be neglected. The method in most common vogue of testing gastric motility is the administration of a meal and the use of the stomach tube to ascertain whether food remnants are present after the lapse of a certain time. The following citations will give a fair idea of this method.

2 Cannon, W. B. *The Mechanical Factors of Digestion*. New York, Longmans, Green & Co., 1912, p. 84.

Kemp³ remarks that the impairment of the motor power is fully as important, if not more important in many cases than damage to the secretory functions. He describes various test-meals used in gastric analysis including those of Riegel,⁴ Ewald,⁵ and Leube⁶ and the test-breakfast of Ewald-Boas.⁷ Regarding the specific question of motility he states

If five hours after a test meal, a small amount of chyme is aspirated the motor power is good. If large quantities are found six hours after the meal the motor function is absolutely (or, if stenosis, relatively) decreased. Some employ the test breakfast. Two hours later the stomach should be empty. If 100 c c or more are found at the end of an hour, or varying quantities at the end of two hours, it shows different degrees of motor insufficiency. The test-meal is more accurate. I sometimes administer a test-supper and aspirate in the morning to test the motor function, following immediately with the test breakfast to examine the secretory function.

He also describes without comment the motility tests with salol (Ewald and Sievers⁸), iodopin (Heichelheim⁹) and oil (Klemperer¹⁰).

Bassler¹¹ mentions as of value the Leube-Riegel test-dinner, consisting of beef-broth, 400 c c, beef, 150 gm, puree or mashed potatoes, 50 gm, and a roll of wheat bread. The exit of this meal from the normal stomach should occur within five hours. But he goes on to say

A word of caution should here be given in assuming the existence of pathologic conditions when five or six hours afterward small quantities of food are extracted, for, while the great bulk of the meal is gone, tarrying remnants of food may be present even in the perfectly normal stomach up to the sixth and even the seventh hour after the time of ingestion. If at the sixth, seventh or eighth, and so on, hour of extraction after the taking of a mixed meal, considerable quantities of the meal constituents are obtained from a stomach, the existence of the following conditions should be considered, namely: Pyloric obstruction, states of atony, a more or less low state of digestive disturbance from degrees of subacute and chronic gastritis accompanied with poor stomach function, and the existence of neurotic conditions of a depressing type affecting the entire motility of the organ. Another form of examination by the extraction of stomach food contents to diagnose pyloric obstruction from

3 Kemp, R. C. *Diseases of the Stomach and Intestines*. Philadelphia, W. B. Saunders Company, 1911, p. 122.

4 Riegel's test-dinner: Meat broth, about 400 c c, beefsteak, 150 to 200 gm, mashed potatoes, 50 gm, and a roll (35 gm).

5 Ewald's test-meal: Finely chopped meat, 175 gm, stale bread, 35 gm, and butter.

6 Leube's test-meal: A plate of soup, a beefsteak and a roll.

7 Ewald and Boas' test-breakfast: One or two rolls (35-70 gm), one cup of tea or water (300-400 c c), given in the morning in the fasting condition.

8 Ewald and Sievers: *Zur Pathologie und Therapie der Magenectasien*. *Therap. Monatsh.*, August, 1887.

9 Heichelheim: *Ztschr. f. klin. Med.*, 1900, p. 321.

10 Klemperer: *Ueber die Motorische Tätigkeit des Menschlichen Magens*, *Deutsch. med. Wchnschr.*, 1888, No. 47.

11 Bassler, A. *Diseases of the Stomach and Upper Alimentary Tract*. Philadelphia, F. A. Davis Co., 1913, p. 158.

any cause (particularly its high degree seen in malignancy) should be mentioned. In this the generally employed procedure is to advise the patient to eat a full meal in the early evening, and then to wash out his stomach the following morning—about ten or twelve hours afterward. Should the patient not have vomited during the night, and food remnants be found in the morning, bona fide pyloric stenoses can almost invariably be diagnosed.

He states further that a simplification of this method, which he can endorse as of much value, is the eating of several raisins¹² in the evening and noting if their skins or seeds are obtained in the morning lavage water. While in this test the obtaining of vegetable skins is of much significance a negative result does not always mean that no stenosis exists. A less complete degree of stenosis, particularly in the pyloric region but not directly at the pylorus, may give positive results with the six, seven or eight-hour extraction of the mixed meal, but a negative finding with the raisin-skin method. The matter, he thinks, is entirely one of degree of stenosis, the nearer the stenosis to the pylorus, the more accurate are the results by both methods, the less the degree of the stenosis, or the farther away from the pylorus it is situated, the better is the result from the mixed meal, and the less so from the raisin-skin method.

Einhorn¹³ gives a fair summary of gastro-enterologic methods in common use when he says

The best and easiest way to test the motor function of the stomach is to examine this organ by means of the tube and lavage in the morning in the fasting condition after the ingestion of a substantial supper on the night previous. Normally the stomach is empty, and therefore when the organ is found to contain a quantity of food, this is the best sign of retarded motion.

ROENTGENOLOGIC TESTS OF MOTILITY

Since the first employment of the Roentgen ray in conjunction with an opaque meal for the diagnosis of gastro-intestinal disease, more or less attention has been directed to gastric motility. By a few men this feature of the examination is considered almost indispensable, by others it is regarded as of secondary importance though usually given some attention, while a few deem it of little moment.

As might be expected, an investigation of the technic used by different roentgenologists shows considerable variance. Wide differences are noted as to

- 1 The opaque salt used
- 2 The character of the vehicle

¹² Bassler speaks of this as the "Mayo method." In fairness it should be said, however, that the addition of raisins to the Riegel meal is credited by Cohnheim (*Diseases of the Digestive Canal*, Edit 2, Philadelphia, J B Lippincott & Co, 1911, p 35) to Boas and Strauss.

¹³ Einhorn, M. *Diseases of the Stomach*. New York, William Wood & Co, 1911, p 119.

3 The proportion of opaque material to the medium of suspension

4 The total quantity administered

5 Management of the patient with regard to eating after the opaque meal has been taken

Bismuth subnitrate, which was used in the first examinations of the human digestive tract, produced toxic results in a few instances, and was superseded by bismuth subcarbonate or the carbonate as it is called in Europe. A little later the oxychlorid of bismuth was used to some extent. On the continent a few have employed zirconium oxid. During recent years chemically pure barium sulphate has come into extensive use. So far as we are able to discover from the published observations of others and from our own experience there seems to be little difference in the evacuation time of the various bismuth salts when given under equal conditions, but the difference in this respect between bismuth salts and barium sulphate is marked, the latter leaving the stomach distinctly earlier. Groedel's¹⁴ figures indicate that with barium sulphate the stomach empties itself twice as fast as with bismuth.

The vehicles employed have been of every sort conceivable, including water, milk, mucilage of acacia, bread and milk, cereal porridges, paps and gruels, mashed potatoes, fermented milk, and mixed meals containing meat. The proportion of opaque salt to suspension medium varies from 10 to 50 per cent of the former, and the total quantity of the meal given ranges from 6 to 20 ounces or more. Finally, practice differs as to permitting the patient to follow his accustomed habits of eating and drinking during the period of examination. Often this important feature is not mentioned, yet it is known that the taking of food after ingestion of the opaque meal will markedly prolong the evacuation time of the latter.

It is quite apparent that from these differing technics, differing results must follow and this undoubtedly accounts very largely for the varying esteem in which Roentgen tests for motility are held.

The prototype of all the opaque meals now in use was that devised by Rieder,¹⁵ and consisted of 50 gm of bismuth carbonate in 350 gm of flour-pap. Rieder considered three to four hours as the normal emptying time for this meal. Commonly half the meal is discharged within an hour. Toward the end of digestion, he remarks, there is a distinct slowing of emptying which he thinks is due to an intestinal reflex. He mentions the experiments of Wulach showing the emptying time of carbohydrate mixtures to be from two and one-half to

14 Groedel, F. The Influence of Various Contrast Substances on the Motility of the Intestinal Canal, *Arch Roentg Ray*, April, 1913, p 420

15 Rieder, H. Das Roentgen-Verfahren im Dienste der Pathologie und Therapie des Magen-Darm-Kanals, *Verhandl d xxix deutsch Kong f inn Med*, J F Bergmann, Wiesbaden, 1912, p 22

three and one-half hours, albuminous mixtures five or six hours, and fat from seven to eight and one-half hours. The Roentgen method gives a good picture of gastric motility. But, Rieder adds, in spite of the great excellence of the Roentgen motility test, the method formerly used alone of withdrawing a test-breakfast or test-meal will firmly retain its diagnostic worth because it will show in every case not only the motility but also the secretory function.

Barclay¹⁶ has used bismuth carbonate in the proportion of 1 to 2 or 3 of the excipient, for which latter he employs bread and milk, thoroughly mashed up, or porridge. The total quantity given varied from 2 to 12 ounces. With regard to motility he says

Retention of bismuth food is the result of pyloric obstruction and Rieder laid it down that the whole of a bismuth meal should have left the stomach within five hours. For diagnostic purposes this is a good enough guide, but I never report definite obstruction unless the delay is well marked. In hospital practice eight hours retention is my standard, but in the vast majority of the cases recorded, some food was still present in the stomach after twenty-four hours. In private practice six hours is my standard, but I always repeat the observation on at least one occasion to verify this finding when the margin of delay is so small.

Groedel¹⁷ at first employed the Rieder carbohydrate meal. An emptying time beyond four hours he regarded as abnormal. Later¹⁸ he began using barium sulphate 250 gm, mixed with 20 gm each of maize flour, sugar and cocoa in 400 c c of water. This meal, he found, emptied normally in two hours.

Kaestle¹⁹ considers two and one-half to three and one-half hours as the normal emptying time of a fluid, carbohydrate (mondamin), contrast meal containing zirconium oxid and weighing 400 gm. A stiff mixture of the same weight may require four hours. Slight delay of evacuation of the fluid meal, up to six hours, he states, may be caused by gastric atony, hyperacidity, reflex pylorospasm, and even beginning pyloric stenosis. Residues after twelve hours or longer occur only with organic pyloric stenosis. Hypermotility may result from a gaping pylorus or strong expulsive energy (hypertonus and hyperperistalsis).

Satterlee and LeWald²⁰ in their description of the water-trap stomach remarked the occurrence of a residue from the bismuth meal

16 Barclay, A. E. *The Stomach and Esophagus*. New York, MacMillan Co., 1913, pp. 9, 36.

17 Groedel, F. M. *Atlas und Grundriss der Roentgendiagnostik*. Munich, J. F. Lehmann, 1909, pp. 176, 198.

18 Groedel, F. M. *The Influence of Various Contrast Substances on the Motility of the Intestinal Canal*, *Arch. Roentg. Ray*, 1913, xvii, 420.

19 Kaestle, K. *Lehrbuch der Roentgenkunde* (Rieder-Rosenthal). Leipzig, J. A. Barth, 1913, p. 531.

20 Satterlee, G. R. and LeWald, L. T. *One Hundred Cases of Water-Trap Stomach*, *Jour. Am. Med. Assn.*, 1913, lxi, 1340.

in many of these cases "The water-trap stomach," they say, "might almost be considered as a ptosed organ, with the first portion of the duodenum and the pylorus fixed in proper position, giving the characteristic long pyloric arm and resemblance to a water trap" The meal given consisted of 90 gm of bismuth subcarbonate suspended in 600 c c of fermented milk A residue from this meal, "long after the usual emptying time" was noted in 50 per cent of the cases In their conclusions they state "The typical water-trap stomach of marked degree, which shows a large residue in the stomach after six hours should be operated on when diagnosed"

Cole²¹ remarks

I have already shown the fallacy of testing the gastric motor efficiency by administering bismuth suspended in fluid or mixed with cereal, and the same is true for intestinal motor efficiency If the test is to be of value the stomach and intestines must be called on to evacuate such a meal as is normally imposed on them Therefore, the true test of gastro-intestinal motor efficiency is made by administering bismuth or barium suspended in fluid, preferably buttermilk, in conjunction with a Riegel meal of meat, potatoes and bread If the stomach is high and of the cow-horn type, especially if a condition of diminished acidity or achylia exists, evacuation will be accomplished very rapidly, perhaps in two hours, whereas many a stomach presenting no organic obstruction requires six hours for complete evacuation

Baetjer and Friedenwald²² gave a meal consisting of bismuth subcarbonate, 1½ ounces, in an ordinary glass of water (about 12 oz) with sufficient mucilage of acacia to make an emulsion In obstruction from within (pyloric carcinoma, ulcer with cicatrix, idiopathic thickening of the pylorus) they noted gastric retention for from ten to twenty hours In obstruction from adhesions from chronic appendicitis or after appendectomy, retention for from six to eight hours was found Gallbladder adhesions showed residue in the stomach after five or six hours Retention from muscular relaxation (atony) was also observed, but the time factor is not given They regard from three to four hours as the normal emptying time for a horizontal stomach, from five to six hours for a prolapsed fish-hook stomach

George and Gerber²³ call attention to the fact that the original Rieder meal contained 40 gm of bismuth subcarbonate in about 300 c c of cooked cereal Later other mediums and much larger amounts of the opaque salts came into use

21 Cole, L G Relation of Lesions of the Small Intestine to Disorders of the Stomach and Cap as Observed Roentgenologically, *Am Jour Med Sc*, 1914, cxlviii, 92

22 Baetjer, F H, and Friedenwald, J On the Diagnosis of Incomplete Forms of Pyloric Stenosis by Means of the Roentgen Ray, *Boston Med and Surg Jour*, 1914, clxvi, 261

23 George, A W, and Gerber, I The Roentgen Diagnosis of Duodenal Ulcer, *Surg, Gyn and Obst*, 1914, xix, 395

As a result of the marked variation of bismuth it is impossible to use the same functional data for diagnosis. This is a point which has not been appreciated by many roentgenologists. They have used various kinds of meals—not only buttermilk, but malted milk, plain milk, water, mashed potato, etc., and have varied the amount of bismuth or barium, and yet have attempted to apply to their work the conclusions based on the observation of functional disturbances in thousands of cases done under the Rieder technic. Obviously this is incorrect. The only proper course left for one who wishes to use these functional data is to accumulate a large number of cases, done with more satisfactory mixtures and check them up with operative results.

In a paper written a few months prior to the above, George and Gerber²⁴ venture this statement: "The more we have accumulated evidence on this subject, the more we have become convinced that six-hour gastric stasis is the least important factor in Roentgen bismuth diagnosis." Recently they²⁵ have reiterated this opinion. It should be noted that with their technic the patient is permitted to take food during the six-hour period.

White and George²⁶ observe that ulcer in some other part of the stomach may cause such spasm of the pylorus that bismuth is retained from two to four times the normal, even up to twenty-four hours, while operation shows the pyloric walls perfectly normal. A considerable residue in the stomach at the end of six hours, with no anatomic defect and nothing found elsewhere to explain it, suggests gastric ulcer, but it is to be remembered that the stomach empties itself entirely in six hours in about one-half the cases of gastric ulcer. These authors state further that the emptying of the stomach depends on several more or less opposing factors, namely, gastric peristalsis, mechanical obstruction at the pylorus or in the duodenum, and the reflex control of the opening and shutting of the pylorus. Ulcer of the duodenum may disturb this reflex, and when acid chyme is squirted into the duodenum the absence of the reflex allows the pylorus to remain open or relaxed, and thus permits rapid emptying of the stomach. They go on to say that when indurated duodenal ulcer or scar tissue or adhesions cause mechanical obstruction, the result depends on the balance of the opposing forces, the stomach emptying in the normal time or earlier or later, according as the obstruction overcomes the tendency to rapid emptying which results from active peristalsis or interference with the pyloric reflex.

24 George, A. W. and Gerber, I. The Practical Application of the Roentgen Method to Gastric and Duodenal Diagnosis, *Jour. Am. Med. Assn.*, 1914, lxii, 1071.

25 George, A. W., and Gerber, I. Observations from the Study of a Thousand Gastrointestinal Cases, *Am. Jour. Roentgenol.*, 1915, ii, 592.

26 White, F. W., and George, A. W. The Roentgen Ray Method in the Diagnosis of Gastric and Duodenal Ulcer, *Boston Med. and Surg. Jour.*, 1913, clxiv, 157.

As a test of motility in those cases in which the stomach tube is contraindicated or refused, Bassler²⁷ uses a mixed-meal method by which he gives 25 gm of bismuth subcarbonate with the Riegel meal and examines by the Roentgen ray six hours later, at which time the stomach should be empty. In marked pyloric stenosis he has noted a residue at twelve hours, or much later, even to five days. However, in a subsequent publication, Bassler²⁸ has this to say:

In the study of motility and exit from the stomach in 203 cases of distinct gastroparesis, in which hourly Roentgen ray observations were made, the conclusion was plain that the Roentgen ray method of diagnosing stasis in the stomach is not as practical as the test-meal method. One hundred and twenty-six of these cases examined by the bismuth-Roentgen-ray method showed delay of exit of six hours or more, while only thirty-one showed the delay by the test-meal method. Instances were encountered in which bismuth was present in the stomach as late as eighteen hours after ingestion, while the stomach on a mixed meal was empty in four and one-half hours.

It is apparent, whatever has been advanced to the contrary, that the method of examination by food extraction is decidedly more to be depended on in gaining an idea of exit from the stomach than is the bismuth Roentgen ray method, for it was strongly suggested that foods pass from the stomach in decidedly less time than will bismuth or any other form of metal salts used to throw a shadow, probably because of the pulverized salts adhering to the mucosa.

The most faithful advocate of the Roentgen motility test is Haudek,²⁹ and to him we are indebted for the double-meal method of examination, the establishment of the six-hour limit and a vast deal of information concerning the significance of disordered motility as shown by the Roentgen ray. The rather chaotic application of the Roentgen examination for motility led Haudek, in 1909, to establish his double-meal method, partly with the view of saving time and partly to make the test more precise. Accordingly, he began the administration of a Rieder meal in the morning, and examined the patient six hours later, at which time a second Rieder meal was given to complete the examination. The selection by Haudek of six hours as the division line between normal and delayed emptying was explained by him on the ground that while the normal stomach will drive out a Rieder meal in about three hours, as an average, delay to five or six hours might result from physiologic causes. He cited as examples the influence of rest and movement, right and left-side positions, psychic factors, eating or drinking after taking the meal, and sedimentation of the opaque salt

27 Bassler. *Diseases of the Stomach and Upper Alimentary Tract*. Philadelphia, F. A. Davis Company, 1913, p. 213.

28 Bassler, A. Some Recent Conclusions on Abdominal Roentgen Ray Work, *Jour. Am. Med. Assn.*, 1913, 1:1, 2217.

29 Haudek, M. Die Technik und Bedeutung der Radiologischen Motilitätsprüfung, *Verhandl. d. xxix. Deutsch. Kongr. f. inn. Med.*, J. F. Bergmann, Wiesbaden, 1912, p. 143.

Even after six hours or longer minute residues might sometimes be found in normal stomachs, and he accordingly ignored mere traces. Small residues, up to a quarter of the meal, he deemed, could be due not only to organic pathologic changes but also to hypomotility from atony, hyperacidity, or long *hubhohe*, that is, a long, vertical pars pylorica. Larger residues could be almost certainly ascribed to pyloric obstruction by organic stenosis or spasm from ulcer. He also pointed out that the test did not rest alone on the presence or absence of a residue, but that the position of the "head" of the six-hour meal gave gross information as to motility. Normally at or near the cecum, the "head" would be advanced far into the large intestine by hypermotility or held back in the small intestine by hypomotility. Further, on giving the second meal, there could also be taken into consideration the tonus of the stomach, its peristalsis, the freedom of passage through the pylorus, the *hubhohe*, and thus the total picture would enable an estimation of "the great X of motility, the functioning of the pylorus."

An experience of years with thousands of cases has increased Haudek's confidence in the method. In a recent article, he³⁰ goes so far as to say that the Roentgen determination of the expelling forces of the stomach gives better results than the older methods, and that it is not only exact and reliable but also very simple. He shows that while the clinical examination cannot determine whether the increase or decrease of motility is due to a change of the expelling power or of the resistance, the Roentgen examination can be much more decisive. While he had previously considered atony to be an occasional cause of six-hour retention he now believes that atony, under otherwise normal conditions, causes only a slight increase of evacuation time, usually below six hours. The most important factor for the evacuation of the stomach is the condition of the pylorus. Lessening of resistance produces the picture of pyloric insufficiency, an increase leads to the highest degrees of stagnation. He enumerates the common causes of increased resistance, both organic and spastic, and cites examples as varied by the functional components of motility. He also mentions Sahli's method of testing the motility with sinking and swimming capsules in differentiating between pylorospasm and organic stenosis, also the effect of papaverin in these conditions. By means of Sahli's capsules the evacuation time of water can be shown; this is usually normal in pylorospasm but prolonged in stenosis. According to Holzknecht the administration of papaverin shortens the emptying time in pylorospasm to normal, increases it in stenosis, and has no effect on a combination of the two.

30 Haudek, M. Ueber die Radiologische Prufung der Magenmotilitat und Ihre Resultate, Fortschr. a. d. Geb. d. Roentgenstrahlen, 1914, xxi, 472.

For more than two years past our work has been based on the double meal method of Haudek, and we can unreservedly endorse his claims. For various reasons we have found it advisable to modify his technic in some particulars, but have retained the six-hour limit and adhered rather closely to his general principles. A cereal porridge instead of a pap for the six-hour meal is employed and barium sulphate³¹ substituted for bismuth salts. Since barium leaves the stomach earlier than bismuth we believe that a six-hour retention of barium is even more significant than one of bismuth. Until the first of this year patients were required to take castor oil on the evening previous to the day of examination, but this has been abandoned as unnecessary. The observations of Hayes³² show that purgation results in a heightening of gastro-intestinal motility for a day or two. A comparison of our observations during the past few months with those made previously, indicates that this increase does occur, but that it does not materially affect the six-hour test. Our present routine is as follows.

The patient comes to the laboratory in the morning without breakfast, and usually, but not always, after tubing and lavage by the gastro-enterologist. He is given a meal consisting of 4 ounces of well-cooked wheaten breakfast cereal with 2 ounces of barium sulphate, to which he is permitted to add a little milk and sugar according to his taste. He is instructed to take neither food nor drink, except water, until the examination is finished. Six hours later he returns and the screen examination is begun. The presence or absence of a residue in the stomach from the motor meal is noted. The amount of retention is recorded on a scale of four units, each unit representing approximately a fourth of the meal. If the entire meal has passed into the intestine its position and distribution are observed. The patient is then given 2 ounces of barium sulphate stirred up with 8 ounces of water. Usually some of this escapes or can be driven through the pylorus, showing its condition as to patency. To complete the examination and to fill the stomach for roentgenography, the patient takes about 12 ounces of a potato-starch pap containing approximately 3 ounces of barium sulphate, after which the behavior of the stomach in all respects is watched.

Our gastro-enterologist's routine for examination of the gastric contents is the following. At 6 p. m. previous to the day of examination the patient takes a modified Riegel meal, that is to say, he is instructed to eat an ordinary meal which must include bread, meat

31 As is well known by roentgenologists, only chemically pure barium sulphate is used, other salts of barium being absorbable and toxic.

32 Hayes, M. R. J. *Roentgen Rays in the Diagnosis of Abnormalities of the Intestinal Tract*, Clin Jour, 1914, xliii, 529. *Abstr Surg, Gyn and Obst*, 1915, xx, 138.

and potatoes. An hour later he eats 20 raisins, the skins of which are easy of identification, and tend to remain in the stomach somewhat longer than the usual food materials. The gastro-enterologist's examinations are begun the next day, about 8 a. m., and, depending on the number of patients to be examined, the interval after the motor meal varies from fourteen to sixteen hours. The estimate of motility is based on the presence or absence of food bits or raisin skins from this meal as shown by tubing at the morning examination. Residues are recorded on a scale of 4. The gastro-enterologist's technic also includes the administration of a modified Ewald test-breakfast for the chemical examination, but with this we are not here concerned.

COMPARISON OF THE RESULTS IN 950 CASES

During the year 1914, 950 patients who had been examined both by the Roentgen ray and the test-meal went to operation. Two hundred and twenty of these, or 23.1 per cent, showed a gastric residue, at the Roentgen-ray examination, from the six-hour meal. One hundred and thirty-one, or 13.7 per cent, had food remnants. In other words, the Roentgen ray showed approximately 70 per cent more retentions than did the clinical test-meal. The lesions found were: Disease of the appendix, 125 cases, disease of the gallbladder, 311; gastric ulcer, 109, gastric cancer 137, duodenal ulcer 268. The accompanying table shows the incidence of retention in each of these conditions, as shown by the Roentgen ray and stomach tube, respectively. The preponderance of six-hour barium residues over food remnants from the test-meal is noteworthy, being twice as great in gastric ulcer and lesions of the gallbladder, almost twice as great in duodenal ulcer, and half again as large in gastric cancer. In the 125 cases with lesions of the appendix, a retention was noted by the Roentgen ray in only one case, and found in two cases only by the stomach tube. In only 12 of 311 cases with lesions of the gallbladder was retention noted either by the Roentgen ray or by tubing. The vast majority (209 or 90.4 per cent) of the 220 patients showing a barium retention, were found at operation to have cancer or ulcer of the stomach, or ulcer of the duodenum.

In 16 cases representing all five conditions, the stomach-tube revealed food remnants, while no six-hour retention of barium was found by the Roentgen ray. On the other hand, 105 patients had Roentgen residues but no food remnants.

In eight of the cases tabulated under gastric ulcer there was also duodenal ulcer. All of these patients showed a residue from the barium meal, and six of them had food remnants.

INCIDENCE OF RETENTION OF TEST-MEAL IN 950 CASES

	Total Number	With Residue (X-Ray)		With Food Remnants (tube)		With Residue (X-Ray) only		With Food Remnants (tube) only		With Both Residue (X-Ray) and Food Remnants (tube)		Number Without Residue (X-Ray) or Food Remnants (tube)	No With Residue (X-Ray) or Food Remnants (tube) or Both
		No	%	No	%	No	%	No	%	No	%		
Lesions of the appendix	125	1	0.8	2	1.6	1	0.8	2	1.6	0	0.0	122	3
Lesions of the gall bladder	311	10	3.2	5	1.6	7	2.2	2	0.6	3	0.9	299	12
Gastric ulcer	109	50	45.8	25	22.9	29	26.6	4	3.5	21	19.2	55	54
Gastric cancer	137	83	60.5	57	41.6	29	21.1	3	2.1	54	39.4	51	86
Duodenal ulcer	268	76	28.3	42	15.6	39	14.5	5	1.8	37	13.8	187	81
	950	220	23.1	131	13.7	105	11.0	16	1.6	115	12.1	714	236

Besides the cases tabulated above, residues were found by the Roentgen ray in one patient in each of the following conditions: Cancer of the pancreas, tumor of the ileum, cancer of the common duct, hydronephrosis, tumor about head of pancreas, tumor of left kidney, subdiaphragmatic abscess, and cancer of the ascending colon. In the four first mentioned, retention was also noted by the gastro-enterologist.

How can the discrepancy between the gastro-enterologist's results and our own be explained?

First, it would seem probable that the time elapsing between the ingestion of the gastro-enterologist's meal and its withdrawal is too liberal, and that the stomach was empty in many cases, although an actual and pathologic hypomotility existed.

Secondly, it is quite possible that the tube may have failed occasionally to bring up food remnants which were present. Harmer and Dodd,³³ by watching with the Roentgen ray the introduction of the tube, frequently noted that the tip impinged against the gastric wall, well above its most dependent portion, and continued efforts to pass the tube simply caused it to curl and displace the tip further upward. In other instances it was found that by passing the usual length of tube in cases of ptosis, the tip might fail to reach the residuum. This, they believe, is a common error. The posture of the patient and the position the stomach occupies in the abdominal cavity affect the success of tubage. From their observations they regard it as "obvious that failure to recover gastric residuum with the unaided stomach tube from a fasting stomach or after the ingestion of a test-meal cannot be accepted as conclusive evidence of the absence of gastric stasis." Reh-fuss, Bergeim and Hawk³⁴ have employed a tube devised on the principle of the duodenal tube, with a slotted metal tip, which by its weight will seek the most dependent part of the stomach. In instances in which the passage of the ordinary tube failed to disclose any residue, the new tube obtained considerable amounts. They found, further, in a series of healthy persons, that the fluid residuum in the normal empty stomach far exceeded the accepted limit of 20 c c, and in several was above 100 c c.

Thirdly, the tube may have failed to reach food retained in the lower loculus of an hour-glass stomach. It seems probable that this occurred in at least one instance of hour-glass stomach where the

33 Harmer, T. W., and Dodd, W. J. Sources of Error in the Use of the Stomach Tube for Diagnosis. Preliminary Report, *THE ARCHIVES INT. MED.*, 1913, **LII**, 488.

34 Reh-fuss, M. E., Bergeim, O., and Hawk, P. B. Gastro-Intestinal Studies. The Question of Residuum Found in the Empty Stomach, *Jour. Am. Med. Assn.*, 1914, **LIII**, 11.

Roentgen ray showed a residue, but the gastro-enterologist reported none

Fourthly, marked differences as to the quantity and character of the food taken by the patient may have affected the gastro-enterologist's results

Fifthly, in exceptional instances of organic stenosis at the pylorus (cancer or ulcer) the tube found retained raisin-skins when the roentgenologic test failed to show a barium retention. It is clear that a stenosis might be sufficiently narrow to block the passage of these skins yet permit a fair exit of finely divided barium

APPLICATION OF THE ROENTGEN TEST

It is evident that the double-meal method does not, as a routine, concern itself with hypermotility in terms of exact time of evacuation, although this can be established with either the first or the second meal if desired. As a rule, the degree of hypermotility can be reckoned by the advance of the head of the first meal beyond the cecum, plus the freedom and continuity of exit of the second meal through the pylorus. It is true that the position of the six-hour meal is the net result of the motility both of the stomach and intestine, but in the absence of intestinal obstruction as shown by other Roentgen signs, or severe obstipation or diarrhea as indicated by the anamnesis, the intestinal factor can be disregarded.

In the presence of an evident hypermotility we have to consider as possible causes duodenal ulcer, gastric carcinoma, anacidity and diarrhea. The report of the gastric analysis or the clinical history will decide as to anacidity or diarrhea, respectively. The most typical hypermotility is seen in cancer with its gaping pylorus which may be infiltrated and stiffened or merely relaxed by the anacidity. The flow through the pyloric opening is continuous and frequently voluminous, and the six-hour meal may have advanced into the transverse colon or beyond. The hypermotility of gastric cancer is not incompatible with actual narrowing of the pylorus, which remains steadily open and thus more than compensates for the narrowing. Over 90 per cent of the gastric cancers will reveal direct Roentgen evidence (filling defects), so that hypermotility is by no means a principal sign. The hypermotility of duodenal ulcer is commonly attributed to interference with the pylorus-closing reflex as well as to hypertonus and hyperperistalsis. Here, again, these factors may balance or even overcompensate a slight organic or spasmodic stenosis at the site of the ulcer. In any event, most of the cases of duodenal ulcer will show hyperperistalsis or other diagnostic signs in the way of an accessory pocket or deformity of the bulb.

An initial rapid rate of clearance of the second barium meal through the pylorus is not alone a dependable sign of hypermotility, the advancement of the six-hour meal in the colon should also be considered. We have seen numerous cases of cholecystitis (with and without periduodenal adhesions) chronic appendicitis, hypochlorhydria from all causes, and general reflex gastrosplasm, in which the clearance was large and uninterrupted during five or ten minutes' examination, yet this clearance was probably not characteristic of the whole period of digestion, since the six-hour meal was not advanced beyond its average position.

By the process of elimination few cases of actual hypermotility remain unexplained, and on the whole, it is of less practical importance than its converse.

With the stomach empty at the end of six hours and the head of the motor meal anywhere from the cecum to the hepatic flexure the gastric motility is considered normal, at least so far as the net result is concerned. It does not follow that this finding absolutely excludes any disturbance of either the active or passive factors of motility, since a diminution of one may be offset by an exaggeration of the other. For example, a somewhat stenotic pylorus or duodenum may be balanced by vigorous gastric peristalsis, or an achylia, or a so-called atonic stomach with weak peristalsis may evacuate its contents through an unusually patent pylorus in average time. Hence a stomach that is empty at six hours, with the motor meal at or not far beyond the cecum, is, strictly speaking, normal as to motility only on condition that other elements are normal also, that is, acidity, peristalsis, tonus and pyloric functioning. If any of the latter are definitely abnormal, the presumption is that one abnormality is compensated by some other, and an analysis of the complication may promote diagnostic nicety. With our present limitations, however, a calculation of this sort could easily lead to error by its intricacy. Likewise, between the average emptying time of say three hours and the arbitrary limit of six hours allowed for presumptively normal evacuation, is a rather wide zone for the play of physiologic and occasionally pathologic, factors causing hypomotility. It was precisely to make liberal allowance for these that Haudek drew his line at six hours, and for this reason we have adhered to that line, though our meal probably leaves the stomach earlier than Haudek's. If there is error it is, at all events, on the side of safety. For emptying times greater than three hours but less than six hours, there is a host of possible causes, including depressive psychic states, weak peristalsis, hypotonus or so-called atony, high *hubhohe*, ptosis, hyperacidity, reflex spasm of the pylorus and slighter grades of stenosis, whether uncompensated or

only partially compensated. In many cases, although the stomach is empty at six hours, retarded evacuation is evinced by the motor meal lying proximal to the cecum, together, sometimes, with scanty initial clearance of the second meal. Often the cause of this moderate hypomotility is manifest in the form, position, peristalsis or tone of the stomach, or the functioning of the pylorus. In our own experience organic stenoses causing delayed gastric evacuation, but within six hours, have been relatively rare. Shortening the time limit to say five hours in order to detect such cases would probably result in greater error by including physiologic and functional delays.

The six-hour limit allows for delay resulting mainly from weakened active factors of motility—tonus and peristalsis. Delay beyond six hours signifies, as a rule, some disturbance of the passive factor, namely, organic or spastic obstruction at or near the pylorus. It should be reiterated that this delay must be shown by a substantial and visible residue, not mere traces held in the gastric folds, nor a collection in the lower pole so small that it can be seen only with difficulty. With a retention of one-fourth or more of the meal, either obstruction of an organic character probably exists or a serious lesion interfering reflexly with emptying. Among the causes of organic obstruction we have noted duodenal and pyloric ulcer with cicatricial contraction, hypertrophic pyloric stenosis, pedunculated benign tumors (polyposis) pyloric carcinoma, syphilis of the stomach, carcinoma of the upper jejunum, and adhesion bands from inflammatory processes in the right upper abdominal quadrant, usually pericholecystitis. Other causes of obstruction mentioned in the literature are foreign bodies (hair-balls, fruit-stones, etc.), kinking of the prolapsed stomach at its duodenal anchorage, adhesions from chronic appendicitis, and tumors outside the duodenum pressing on it, although we have not encountered a six-hour retention attributable to any of these, except possibly the last.

Small residues down to an eighth or less of the motor meal may, of course, also result from organic narrowing. A more common cause is spasm of the pylorus occurring reflexly from a lesion of the stomach itself, such as ulcer, or from an extrinsic pathologic focus, most often the gallbladder or appendix, and also, but rarely, from more remote abdominal lesions. Holzknicht³⁵ has remarked the possibility of a six-hour bismuth residue from pyloric spasm due to morphinism, or a single administration of morphin at the time of examination.

In explaining the mechanism by which gastric retentions are produced in the absence of an organic stenosis, roentgenologists have frequently assigned "pylorospasm" as a cause. Now, by the clinician,

³⁵ Holzknicht, G. The Roentgen Diagnosis of the Stomach, Arch. Roentg. Ray, 1911, v, 206.

the term is limited to a spasmodic contraction of the pylorus accompanied by pain, vomiting, etc., occurring commonly as a symptom of extragastric conditions, for example, disease of the gallbladder. Roentgenologically, the word has been used rather broadly, perhaps somewhat loosely, to cover an irritable, or hypertonic, or spastic pylorus, which relaxes less freely or less frequently than the normal pylorus, regardless of symptoms. Thus Lippmann³⁶ takes J T Case to task concerning the matter, and goes on to say

Roentgenologists habitually diagnose pylorospasm when they find a six-hour residue in a highly acid stomach showing clinically no signs of pylorostenosis. They know, however, that it cannot be true. Firstly, in the great majority of cases they can press this bismuth through the pylorus into the duodenum by effleurage with the hand or with the distinctor of Holzkecht. Secondly, a jet of bismuth water will often dash through the pylorus into the duodenum although the residue remains. Most important of all, I have often passed the large Gross duodenal tube through the pylorus without any difficulty. I have even passed the tube while the six-hour residue was in the stomach in a few cases. Certainly a pylorus which allows a large lead ball to pass is not inclined to pylorospasm. It seems to me that the residue is due to the sinking of the bismuth in the excessive fluid secretion which is so often associated with gastric and duodenal ulcer cases. Most of the men believe that the residue is due to pylorospasm plus hypersecretion, but in consideration of the facts mentioned above, I believe that pylorospasm in its purely clinical sense is a negligible factor in the ordinary case with a six-hour residue.

As a matter of fact, a pylorus which is not organically stenosed is not infrequently seen to remain closed continuously or for abnormally long periods during the Roentgen-ray examination of anatomically normal stomachs showing a six-hour retention, and whether the term "pylorospasm" be strictly applicable or not, the condition cannot be ignored as a probable cause of gastric retention.

As remarked previously, Haudek has mentioned the high *hubhohe*, that is a long, steeply ascending pyloric arm, as a cause of hypomotility. Of very similar character is the "water-trap stomach" of Satterlee and LeWald, in many cases of which, with their technic, six-hour residues were noted. In both these conditions there is usually a degree of gastric atony. Cannon³⁷ holds that, in the normal stomach, drainage by gravity is an unfortunate conception, that the food is in exact equilibrium and that muscular action is necessary to its progression. Haudek claims, on the other hand, that the existence of an impeding action of a high level of the outlet has been shown experimentally, as there is a shortened evacuation time in the right lateral position and a prolonged evacuation time in the left lateral position.

³⁶ Lippmann, C W. Pylorospasm, Jour. Am Med Assn., 1914, lxii, 2031.

³⁷ Cannon W B. The Mechanical Factors of Digestion. New York, Longmans, Green & Co. 1913. p. 47.

Neilson and Lipsitz³⁸ have found from experiments on healthy young men that lying on the right side produces a more rapid evacuation of water than does any other position, and that lying on the back causes a quicker emptying than the upright posture. In the light of these statements it would appear that while gravity probably plays a minor rôle in gastric evacuation, as compared with other factors, it cannot be altogether disregarded. Whether a high situation of the pyloric outlet, without an associated gastric atony, may or may not cause a delay of evacuation, we have not noted such delay go beyond six hours with the barium meal. Nor have we noted a six-hour residue attributable simply to hyperacidity, atony, or intestinal stasis with or without "kinking of the duodenum." While the motility of the stomach in a given case is susceptible of some variation from time to time, we have seldom seen a six-hour retention which did not recur at a subsequent examination. But, in the case of a residue without any other diagnostic indications, the test with the motor meal should be repeated before drawing conclusions. On the whole it would seem that Holzkecht³⁹ was not speaking extravagantly when he said "Haudek's method of the double bismuth meal has at one step promoted the motility test to the first place in the Roentgen examination of the stomach."

The interpretation of the results from the double-meal method may be either simple or complex as desired. The observer may be content with determining the presence or absence of a residue at the end of six hours. With the presence of such a residue he can be fairly certain of organic pathology somewhere in the gastro-intestinal tract, and probably in the stomach or duodenum. Again, he may also take cognizance of hypermotility or lesser degrees of hypomotility. Still again he may consider the results in the light of all the discoverable factors pertaining to motility, including the gastric form, position, tonus, peristalsis, and acidity. Finally, he may combine and correlate his findings with other roentgenologic signs, the physical examination and the clinical history. By the construction of "symptom-complexes" in this manner Holzkecht³⁹ was enabled to make diagnoses which otherwise could not be made, and we have routinely followed this plan to advantage. While this has been criticized as an "indirect" method in comparison with the "direct" method, namely that of proving the presence of a lesion by showing local deformity of contour, we can only say that we have often failed to discover such deformity although

38 Neilson, C. H., and Lipsitz, S. T. The Effect of Various Procedures on the Passage of Liquids from the Stomach, *Jour Am Med Assn*, 1915, *lxiv*, 1052.

39 Holzkecht, G. The Roentgen Diagnosis of the Stomach, *Arch Roentg Ray*, 1911, *xv*, 206.

the symptom and sign-complex established the diagnosis. Certainly deformity of contour is of the highest roentgenologic value and should be zealously sought for, but, like all other signs it fades gradually into the realm of uncertainty. A six-hour residue is a strong stimulus to careful search for direct signs, and, if the latter are found, the presence of a retention is added assurance that the eye is not deceived, that a lesion exists and that it is interfering with motility, which latter information is important to the surgeon. A diagnosis which takes into account all the facts obtainable from all sources is less likely to go astray than one which rests on a single phenomenon.

Gastric retention can be combined into various indicative complexes. A six-hour residue with a stomach of normal contour, showing hyperperistalsis, means obstructive duodenal ulcer more than ninety times out of a hundred. Residue plus an apparently normal gastric outline, plus an irregular, vigorous peristalsis, chiefly on the greater curvature, usually signifies a lesion involving the pylorus. A residue with an achylia, but without gross alteration of the gastric contour, should suggest the probability either of a small obstructing pyloric carcinoma, or obstruction of the duodenum by pericholecystic adhesions, careful attention to the pyloric and duodenal contours will usually make the distinction. Residue with hyperacidity and no irregularity of the gastric or duodenal outline would indicate a stomach reflexly affected by some other abdominal condition, notably cholecystitis or appendicitis. Innumerable but practicable complexes can be formulated by the introduction of other related data. We have on other occasions emphasized the importance of a general correlation in every case.

The possibilities of the roentgenologic estimation of motility are by no means exhausted. The method described in detail deals with the evacuation of a carbohydrate meal only. We can freely endorse its convenience and trustworthiness in the diagnosis of the graver and usually surgical conditions. By a mixed meal and an extension of the time limit, or by examination at short intervals, or by testing the motility of each individual for carbohydrates, proteins and fats separately, the diagnosis of slighter disturbances of motility, amenable to medical treatment, might be assisted. But, with all the work of the experimental physiologists before us, no meal can be devised the normal emptying time of which can be foretold with certainty, and any test must be proved by trial with an abundant material.

As a caricature may sometimes serve to show the truth better than a photograph, so a diagrammatic representation of motility may assist a clearer understanding. Taking as a basis a meal which leaves the normal stomach in an average time of say three hours, such as

the bariumized carbohydrate meal, we may divide gastric evacuation time as represented on a scale of hours into three zones, viz

- 1 A zone of normal motility
- 2 A zone of pathologic hypermotility
- 3 A zone of pathologic hypomotility

1 The zone of normal motility must extend from an emptying time somewhat less than three hours to an emptying time somewhat greater than three hours, since we can only fix the three-hour point as an average, on either side of which a variation may be due to purely physiologic causes. Within this zone we are also obliged, as a conservative measure, to include slighter tendencies to hypermotility or hypomotility from causes which, though pathologic, are not pronounced or are compensated wholly or in part. General knowledge justifies the assumption that such variation toward hypermotility is not wide, and, for the purpose of this diagram, we may choose the two-hour point as the normal minimum. The variation toward hypomotility we may grant to be much wider, Haudek makes a generous allowance to the end of the sixth hour which we will accept. The contents of this normal zone would then include

(a) Normal motility (Example A normal stomach functioning in a normal manner)

(b) Early emptying, physiologic (Example A hypertonic, steer-horn stomach)

(c) Early emptying, pathologic but partially compensated (Example Duodenal ulcer with obstruction sufficient to prolong the evacuation time to two hours in spite of an associated hyperperistalsis, hypertonus and free pyloric patency)

(d) Disordered motility with abnormal but balanced factors (Example Stenosing carcinoma with achylia, yet with a net emptying time of three hours)

(e) Delayed emptying, physiologic (Example A somewhat hypotonic fish-hook stomach)

(f) Delayed emptying, pathologic, but partially compensated (Example Stenosis with hyperperistalsis, emptying being retarded, but within six hours)

2 The zone of hypermotility, restricted to an emptying time less than two hours, would include such frankly pathologic conditions as nonobstructing gastric carcinoma, duodenal ulcer and diarrhetic conditions

3 The zone of hypomotility, beyond six hours, would comprise the stenoses, both organic and spasmodic, as examples of which may be mentioned obstructing pyloric carcinoma or ulcer, markedly obstruct-

ing duodenal ulcer, and reflex pylorospasm from disease of the gall-bladder, or gastric ulcer remote from the pylorus

As a matter of fact we know that these zones may overlap each other and that time alone will not delimit normal from abnormal motility. The diagram, while somewhat practical in a way, illustrates the time factor only, and, as said before, a final opinion must rest on an analysis of all the factors. By the Roentgen method this analysis is both possible and practicable, and herein lies its superiority to the test-meal and tube

Zone of Hypermotility	{	Hours	
		0	
		1	Early emptying, pathologic (Nonobstructing gastric carcinoma Duodenal ulcer Diarrheic conditions)
Zone of Normal Motility	{	2	Normal emptying (A normal stomach functioning in a normal manner) Early emptying, physiologic (Hypertonic, steer-horn stomach)
		3	Early emptying, pathologic, but slight, or partially compensated (Duodenal irritation Duodenal ulcer with obstruction sufficient to prolong the evacuation time to two hours in spite of associated hyperperistalsis, hypertonus and free pyloric patency)
		4	Disordered motility with abnormal but balanced factors (Stenosing carcinoma with achylia, average emptying time)
		5	Delayed emptying, physiologic (Hypotonic fish-hook stomach)
			Delayed emptying, pathologic, but slight or partially compensated (Slight stenosis Stenosis with hyperperistalsis, evacuation retarded but within six hours)
		6	
Zone of Hypomotility	{		Delayed emptying, pathologic Stenosis
		7	(a) Organic (Obstructing pyloric carcinoma Pyloric ulcer Obstructing duodenal ulcer Periduodenal adhesions, etc) (b) Spasmodic (Reflex pylorospasm from ulcer on the lesser curvature, cholecystitis, appendicitis, and remote abdominal lesions)
		8	
		Etc	

CONCLUSIONS

1 It would seem that the bariumized carbohydrate meal described above is a more sensitive test for gastric motility than the modified Riegel meal as commonly used in the Mayo clinic

2 The roentgenologic double-meal method is more informative than tubing after a motor test-meal, since the former not only shows delay of evacuation beyond six hours, but also yields information as to hypermotile conditions, and often by showing both the active and

passive factors concerned in motility, aids in the judgment of the net result

3 A distinct residue after six hours from the barium meal given under the conditions prescribed has been, nine times out of ten, in our experience, indicative of grave pathology and usually denotes obstruction at or near the pylorus

4 The roentgenologic method is probably capable of further elaboration and refinement. By this means the motility of the stomach for various food-stuffs, given separately and in combination, can be determined with ease and accuracy and by such determinations the diagnosis of gastric disorders might be further promoted

5 The six-hour barium residue may be the most definite and striking roentgenologic sign of a gastro-intestinal lesion. Other signs may be so slight and indefinite that a diagnosis might not be ventured without this retention

6 Retention of the barium meal is often an important element in roentgenologic symptom-complexes as used in diagnosis. In the absence of other decisive roentgen manifestations this finding may have considerable value in correlation with the clinical data

UROBILIN IN THE STOOL IN PERNICIOUS ANEMIA AS INFLUENCED BY SPLENECTOMY, TRANSFUSION AND SALVARSAN †

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On account of the peculiar course of pernicious anemia, characterized as it is by marked remissions, there has always been great difficulty in judging fairly the effect of any method treatment. Brilliant results have been reported in certain cases from almost every therapeutic measure employed, yet it is impossible to say in many of these cases that a spontaneous remission was not beginning at the time of treatment, since the blood picture often fails to give this information. It is therefore desirable that a more reliable method be employed for determining the different stages in the course of the disease.

Since this form of anemia is accompanied by a greatly increased blood destruction, it seems not unreasonable to assume that the quantity of blood being destroyed may be regarded as an indication of the severity of the disease process. This can be determined by estimating the quantity of urobilin in the stool, since it has been shown that the amount of urobilin excreted depends directly on the degree of blood destruction present. In a previous study¹ of the variations in urobilin excretion in a variety of conditions, including both primary and secondary anemia, malaria, jaundice from various causes, cirrhosis, etc., it was found that only those cases which gave evidence of increased blood destruction clinically, showed an abnormal urobilin output. There were eleven cases of pernicious anemia, all of which had an increased urobilin excretion, while on the other hand six cases of secondary anemia all showed a urobilin output within normal limits.

Determinations were made on nine cases of pernicious anemia with the hope of being able to demonstrate some definite effect of treatment on the urobilin output. The estimations were begun in every case before treatment and continued during periods of time lasting from two weeks to three months. Following the different forms of treatment averages of the estimations were made over weekly intervals.

* Submitted for publication May 29, 1915

* From the Medical Wards of the Massachusetts General Hospital

1 Robertson O H. Urobilin in the Stool—An Index to Blood Destruction, *THE ARCHIVES INT MED*, 1915, *xv*, 1072

when possible, as this period of time seemed a fair measure of the effect produced. The method used was that described by Wilbur and Addis,² which consists in extracting the urobilin from the total twenty-four-hourly stool with acid alcohol. This extract is then diluted till the characteristic spectroscopic absorption bands of urobilin disappear and the reading made at this point. Estimations in normal persons average about 5,000 dilutions of the original volume of the stool.

In six of the cases, splenectomy was performed, three received salvarsan, and four were transfused. Of the four cases transfused, one had previously been given salvarsan. The other three were cases of splenectomy who were transfused before operation.

SPLENECTOMY

There are a few cases of pernicious anemia reported in the literature in which quantitative urobilin estimations were made before and after operation. Eppinger and Ranzi³ report the most successful series and in their five patients there was a drop to normal in every instance following splenectomy. In one case the urobilin was still low after seven months. They do not say whether estimations were made later in the other four cases or not. All five showed marked improvement. Huber's⁴ patient still had a high urobilin output five weeks after operation. It was quite evident, however, that blood destruction was still going on, since the red cells showed a marked decrease in number during the ten days following the estimation. Moffitt⁵ reports one case in which the urobilin was still increased one week after operation, but estimations could not be continued as the patient died shortly afterwards from a complicating infection.

McCrudden⁶ found in one case, three weeks after splenectomy, a urobilin output twice as great as it had been before. At the time the estimations were made, however, the red count was falling rapidly. Four months later the patient had shown considerable improvement, the red count was increasing, and the urobilin was found to be normal. A second case showed no benefit from splenectomy and although the urobilin decreased from its high figure given before operation, it did not reach normal.

2 Wilbur, R. L., and Addis, T. *THE ARCHIVES INT. MED.*, 1914, xiii, 235.

3 Eppinger, H., and Ranzi, E. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1914, xxii, 796.

4 Huber, O. R. C. *Berl. klin. Wchnschr.*, 1913, l, 2179.

5 Moffitt, H. C. *Am. Jour. Med. Sc.*, 1914, cxlviii, 817.

6 These two unreported cases are cited with the kind permission of Dr. Francis McCrudden of the Robert Brigham Hospital, Boston.

In the six cases of this series treated by splenectomy,⁷ the urobilin estimation before operation varied from 10,300 to 46,000; the highest was given by Patient 3, who showed the most rapid drop in red count and hemoglobin. Immediately following splenectomy there was a marked diminution in urobilin output which reached normal in all but two cases.

In Case 1 it is seen that the urobilin output three and one-half months after splenectomy was not only normal, but exactly the same as it was immediately afterwards. During this time the number of red cells had increased from 2,500,000 to 5,000,000.

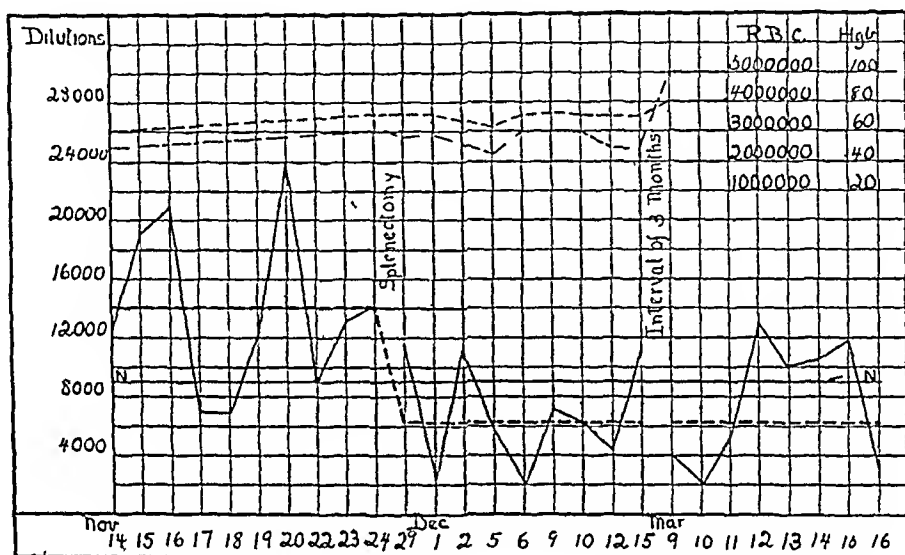


Chart 1 (Case 1) —The curves in this and Charts 2 and 3 have the following significance: ———, daily urobilin excretion, - - - - -, average daily excretion, ·····, upper limit of normal average daily excretion, ———, hemoglobin, ———, red blood cells. N B—The normal average daily excretion is about 5,000 dilutions.

The urobilin in Case 2 immediately before splenectomy was not as much above normal as in the other cases, yet the drop afterwards was quite as definite. At the end of three months, however, the patient showed an output of 14,000. While there was definite improvement both in his general condition and blood, yet the blood picture still showed the characteristic appearance of pernicious anemia and the red cells were slightly under 4,000,000.

Case 3 just before operation gave the exceedingly high estimation of 46,000. There was an immediate drop to 14,600 afterwards, with a subsequent rise to 20,000 at the time of discharge from the hospital. During this time he had shown a striking improvement generally and

⁷ A complete clinical report of Cases 1 to 5 appears in The Journal of the American Medical Association 1915 Ix, 216.

his red cells had reached 4,000,000, but the appearance of the cells was unmistakably that given by pernicious anemia

The chart of Case 4 was almost identical with that of Case 1, except that before operation the urobilin was 13,000 and the red count 1,500,000. Immediately following splenectomy the urobilin dropped to 3,500 and two and a half months later was 7,400. The qualitative and quantitative improvement in the blood was equally as marked as in Case 1.

Case 5 had a red count of about 2,000,000 and a urobilin output of 14,000. Following operation the urobilin dropped at once to 7,900. After two months and a half it had increased to 16,000 which was higher than before operation. He had shown the least improvement of any of the patients and at the time the last estimations were made his red cells numbered only 2,900,000.

Case 6 before splenectomy had a urobilin output of 21,900 and a red count of 1,632,000. This patient showed the same evidence of marked bone marrow stimulation following splenectomy as seen in the other five cases, i. e., the appearance of blasts and Howell-Jolly bodies in the blood. The urobilin dropped to 16,900 but did not go any lower while under observation. The number of red cells at the time of discharge was practically the same as before operation, but there was definite improvement in the general condition. No further estimations have been made, since this patient was the last one of the series operated on and has only just left the hospital.

The marked drop of urobilin in these cases is of considerable significance, since it completes the picture of a beginning remission. The appearance in the blood of blasts and Howell-Jolly bodies indicated bone marrow stimulation, while the decrease in urobilin output indicated an accompanying diminished blood destruction. The return to an increased output in Cases 2 and 5 is in accord with the persistent markedly abnormal appearance of the blood picture. The same may be said of Cases 3 and 6, which showed a definite drop but did not return to normal.

TRANSFUSION

The influence of transfusion on urobilin excretion seems to depend chiefly on the reaction of the patient to the newly introduced blood. Three of the four cases showed a definite stimulation of the bone marrow and in all three the urobilin output was temporarily increased. The fourth showed no such change.

Case 2 showed the most marked stimulating effect of transfusion. The red cells increased from 1,600,000 immediately afterwards to 3,200,000 within six days and there was an accompanying shower of blasts. At the same time the urobilin increased from 17,000 to 22,000.

This case shows quite strikingly how the urobilin output follows the changes in the course of the disease, the beginning remission being accompanied by a drop to normal

Cases 3 and 6 were also transfused. In Case 3 the resulting numerical increase was not marked, but the appearance of blasts made it seem certain that bone marrow stimulation had occurred. The urobilin before transfusion was 30,000, during the week following it was 46,000. At this point splenectomy was done, so it was not possible to observe the effect further. Case 6 showed during the week preceding transfusion, a urobilin excretion of 20,900. During the week

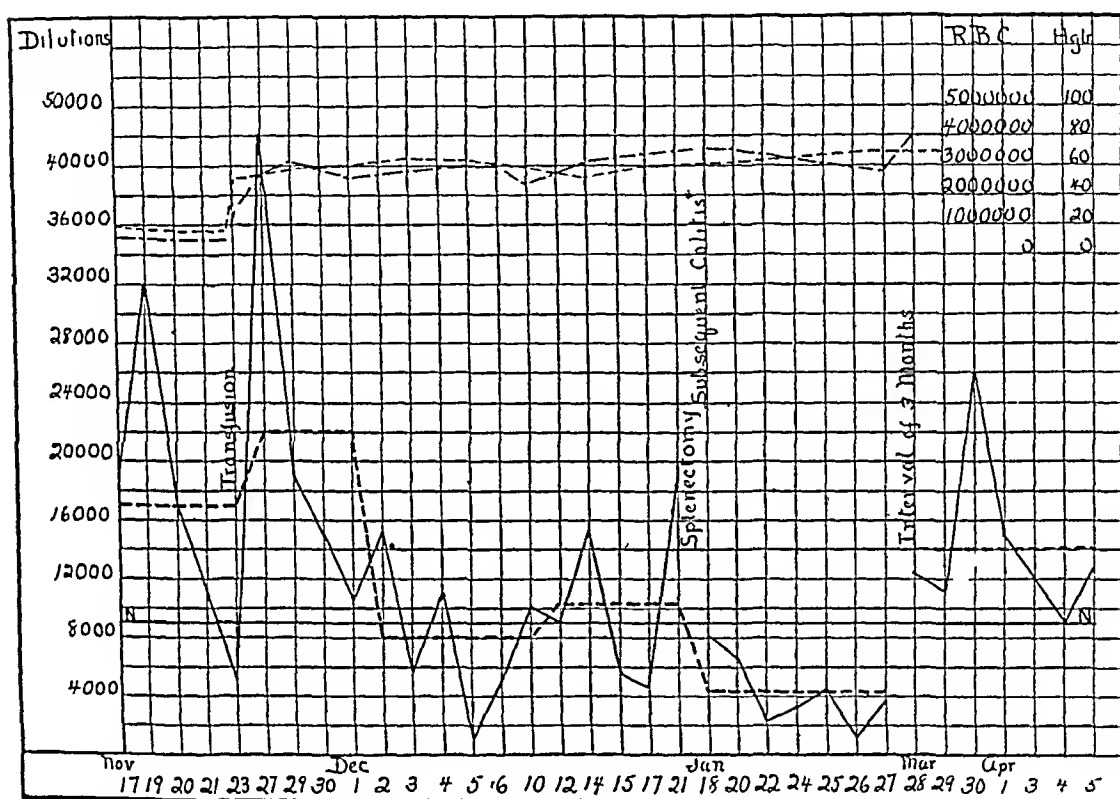


Chart 2 (Case 2) —No tests were made during period of colitis as estimations on diarrhea stools are inaccurate. This is due to the fact that with an increased rate of passage of the bile through the intestinal tract, a smaller proportion of bile than normal is transformed into urobilin.

following, it had increased to 30,000 and at the same time the red cells increased from 1,400,000 immediately after transfusion, to 2,300,000. The patient then had a severe attack of tonsillitis which seemed to check the beginning remission as the blood count ceased to rise and even showed a downward tendency. The urobilin returned to its former level.

Case 7 had received previously several doses of salvarsan. Following transfusion there was no change in the blood other than the temporary increase in the number of red cells due to the newly introduced blood. From the chart one might infer that instead of increasing,

as in the other two cases, the urobilin output was diminished after transfusion. However, on account of the fact that two weeks had elapsed since the last estimation, one cannot say whether the drop occurred before or after transfusion. At any rate it seems quite apparent that there was no increase in urobilin.

SALVARSAN

The administration of salvarsan seems to have no constant effect on urobilin secretion. Case 7, as indicated in the chart, received five injections of salvarsan at weekly intervals. Three of the doses were followed (Chart 3, Case 7) by a drop in urobilin and two by a decided

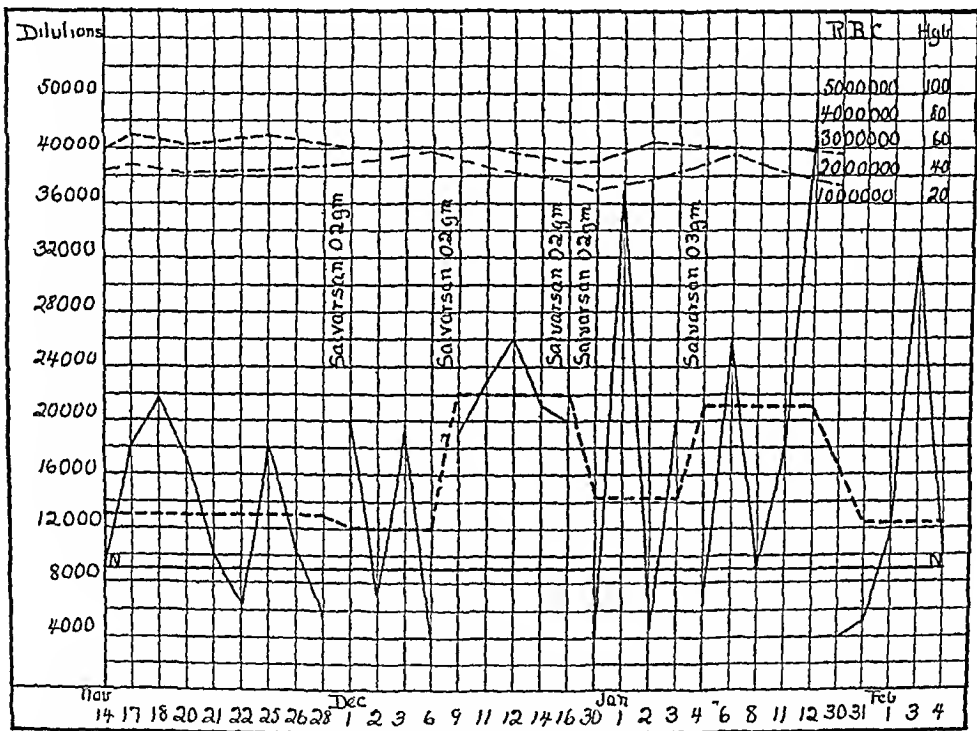


Chart 3 (Case 7) —Urobilin curves during the administration of salvarsan

rise. But it will be noted that accompanying these fluctuations in the urobilin, there were corresponding variations in the red count. When the number of red cells was diminishing there was an increase in the amount of urobilin excreted, denoting a greater blood destruction, while on the other hand, when the red cells began to increase there was an immediate decrease in urobilin, indicating a lessened degree of blood destruction. Since the blood count showed no constant change following salvarsan, we seem justified in concluding that this drug had very little, if any, effect on the urobilin excretion in this case.

Case 8 had an output of 30,000 before salvarsan. During the two weeks following a single dose—0.3 gm—the urobilin dropped to

12,500 This showed undoubtedly a marked decrease in blood destruction. However, a complicating factor entered here in the form of a severe throat infection which began about this time, and produced marked prostration. The patient died at the end of two weeks. A plausible explanation of the decreased urobilin output in this case was a diminished blood production, due to bone marrow injury resulting from extreme toxemia, rather than to any effect of salvarsan.

Case 9 received two doses of salvarsan. Following the first dose there was no change in the urobilin excretion. Estimations could not be made after the second as the patient became incontinent of feces.

This absence of any real effect of salvarsan on the urobilin output coincides with the absence of symptomatic improvement in these patients.

DISCUSSION

From a study of these nine cases it is seen that the effect of treatment on the urobilin is most marked in the cases of splenectomy. Here the drop in urobilin output, occurring long before there was any change in the number of red cells, gave us early information as to the benefit resulting from this procedure. Again, the finding of a high urobilin excretion in several of the cases months after splenectomy, together with the abnormal appearance of the red cells, makes it seem doubly certain that the improvement in these cases is only temporary, in spite of the fact that the number of red cells is well up toward normal.

Judging by the variety of both clinical and blood pictures seen in grave anemia, it seems reasonable to assume that the bone marrow may show varying degrees of functional activity. This may range on the one hand from a markedly hyperactive bone marrow, associated with a great increase in blood destruction, to a very much depressed bone marrow activity on the other, presumably resulting from extensive injury, and unaccompanied by abnormal blood destruction. Splenectomy has been advocated in pernicious anemia on the theory that by taking out the spleen, the chief hemolytic agent is removed. Therefore this operation should have its most marked beneficial effect in those cases in which the anemia is accompanied by a greatly increased blood destruction. Thus, in deciding the advisability of splenectomy it seems fair to regard the urobilin output as one of the important indications of how much benefit may be expected from this procedure. But when the anemia results chiefly from a depressed marrow functioning, we would expect much less benefit from splenectomy, or none at all, depending on the degree of bone marrow injury. This latter type in its most marked form—aplastic anemia—is a rare condition.

SUMMARY AND CONCLUSIONS

1 Splenectomy In six cases of pernicious anemia with splenectomy, the urobilin output which had previously been high, showed a marked decrease immediately after operation. The two cases in which the urobilin later returned to a high figure, as well as one case with a persistently increased output, showed definitely less improvement than the two cases in which the urobilin remained normal.

2 Transfusion Three of the four patients transfused gave evidence of a resulting bone marrow stimulation and at the same time showed a temporary increase in urobilin excretion. The one case in which transfusion was without effect showed no such increase.

3 Salvarsan In three patients treated with salvarsan, there was practically no effect, either on the course of the disease or on the urobilin excretion.

4 It seems fair to conclude that

1 Variations in the urobilin output may be taken as an index of corresponding changes in the course of the disease.

2 Such variations in the urobilin may occur before there is any change in the number of red cells.

3 The determination of the urobilin output as an index of blood destruction is the most accurate means we have of estimating the effect of treatment.

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METABOLISM STUDIES BEFORE AND AFTER SPLENECTOMY IN CONGENITAL HEMOLYTIC ICTERUS *

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AND

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In this communication we present the results of a study of the metabolism, before and after splenectomy, in a child 5 years of age suffering from congenital hemolytic icterus with splenomegaly. As Dr S McC Hamill, to whom we are indebted for the opportunity of making these studies, will, in a later communication, offer a consideration of the clinical and therapeutic problems involved, we will, aside from the metabolic studies, present only a brief abstract of the clinical history, a note on the pathology of the removed spleen and a table (Table 1) of the blood examinations before and after operation.

ABSTRACT OF CLINICAL HISTORY

At birth, at term, the child weighed 7 pounds and is described as lacking the characteristic red color of the newly born. About twenty-four hours after birth the "alabaster whiteness" of the skin, which the mother describes, changed to a mahogany brown which lasted three months, gradually fading to a sallow pallor, which has persisted. At six months, when the child passed through an attack of pneumonia, it weighed only 10 pounds. The general health was poor and gastrointestinal disturbances frequent. In the fourteenth month the first severe anemia, accompanied by dark brown discolorations of the skin and preceded by protracted vomiting and diarrhea, was observed. Two months later a similar attack occurred with the new feature of marked edema of the entire body. During these attacks the rectal temperature usually rose to 104 or 105. Periods of recrudescence and exacerbation followed one another until the child was 2½ years old when an unusually severe attack kept him in bed for five months. Vomiting and diarrhea were severe and hemorrhages from the nose and bowel were frequent and difficult to control. During the second month of this period a partial paralysis of the left side developed. At this time an injection of neosalvarsan was given, more for the hematinic action of the arsenic, than with any suspicion of lues. Gradual improvement

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* From the John Herr Musser Department of Research Medicine, University of Pennsylvania

followed this treatment and after the paralysis had disappeared, except for a residual spastic palsy of the left leg, the child enjoyed fairly good health. The Wassermann reaction frequently repeated has always been negative. During the eight months following this attack, salvarsan was given five times by rectum. About the time he was 5 years old and again seven months later, he lost the power of speech, was more or less delirious and complained of pain in his head. At $3\frac{1}{2}$ and again at $4\frac{1}{2}$ years, he had an otitis media. His appetite has always been poor, never normal, and at times he refused to eat. A tendency to localized edema, especially of the face and of the hand, has been constantly noted. He tires easily and frequently complains of this. Obstinate constipation has been the rule and the feces are described as dark or orange in color.

From the family history, it is found that a sister was jaundiced for ten days and a brother for two days after birth, but these children, now 15 and 13 years of age respectively, have otherwise been in good health. The father is said to have had an enlarged spleen and offers a history of exposure to lues, of skin eruption and chronic abscess of joint and ankle. The mother, three months before the birth of the subject of the present study, was paralyzed and suffered a separation of the pelvic bones. The delivery was under anesthesia.

Laboratory Examinations—An examination of the numerous clinical records which have accumulated shows that the urine offers nothing of unusual interest. The only positive finding is an occasional slight trace of albumin. Tests for bile have always been negative and urobilin tests have shown no increase of this substance. Examinations of the feces indicate that food is well digested, tests for occult blood have been negative and no parasites or ova have been found. No records of the early blood examinations have been preserved, except a brief record that at the time of the first severe attack (when fourteen months old) the hemoglobin fell to 24 per cent and a diagnosis of pernicious anemia was made. A number of counts made during the years 1913 and 1914 showed considerable variation in both hemoglobin (from 65 per cent to 28 per cent) and red blood cells (4,180,000 to 1,360,000). The Brulé test and tests for cross hemolysis with normal serum and cells were negative. (These were performed by Dr. E. B. Krumbhaar.) The subsequent blood counts are summarized in Table 1.

At the beginning (Dec. 3, 1914) of our metabolism studies one of us (O. H. P. P.) made a complete examination of the child, and from the notes at that time, the following abstract of positive findings has been prepared.

The boy is $5\frac{1}{2}$ years of age, 105.5 cm. in height, weighs 39 pounds, is well nourished and of good muscular development. His skin is slightly sallow, but there is no true jaundice. Over the vessels of the neck, a systolic bruit is

heard and an occasional slight systolic whiff is heard at the apex of the heart. At the base of the heart, the first sound is replaced by a systolic murmur of a blowing character and the second sounds are accentuated. Normal sounds are heard at the tricuspid area. The liver is doubtfully palpable. The splenic dulness begins in the midaxillary line at the sixth rib and extends down a little below the line of the umbilicus, its greatest length is 18 cm and its greatest width about 9 cm. The spleen feels firm, smooth and without distinct notches.

The right lower extremity is normal, the left lower extremity normal as to thigh and leg, but the ankle and foot show a spastic paralysis. The urine at this time was amber in color with no gross sediment, the specific gravity was 1029, tests for albumin, sugar, acetone, diacetic acid, indican and bilirubin were negative. The test for urobilin gave a doubtful reaction, under the microscope some mucus was seen but no cells, casts or crystals. The blood count at this time is given in Table 1, under the date of Dec 3, 1914.

The first metabolic period ran from the fourth to the fourteenth of December and during this time there was little or no change in the patient's condition. Throughout the period there was a tendency to elevation of temperature which, however, rose but once over 101. The child was not kept in bed, ate regularly and required no medication or cathartic. At the end of the period, he was discharged to return after Christmas.

During the interval at home (Dec 14, 1914, to Jan 26, 1915), no noteworthy change in condition occurred. On January 26, the patient was readmitted to the University Hospital, service of Dr Charles H. Frazier. Physical examination revealed nothing new, examination of the blood and urine showed but little change. On January 28, the spleen was removed by Dr Frazier, under ether anesthesia. The operation was uneventful and there was only a trifling loss of blood. At the time of the operation the coagulation time of the blood was found to be about four minutes and tests for resistance of red cells showed beginning of hemolysis in 0.65 per cent, and complete hemolysis in 0.425 per cent salt solution. Convalescence after the operation was satisfactory and on February 4, the patient was transferred to the medical service, and the second period of metabolism study was started on February 5. At this time the child's weight was 40 pounds.

On the fourth day of metabolism study, an attack of bronchitis caused a rise of temperature to 103 and for two or three days there was some loss of appetite, and on the ninth day, a mild otitis media developed. Despite these disturbances, the metabolism study was continued until the period of ten days representing the eighth to eighteenth days after splenectomy was completed.

At the end of the period, the child's weight was 38½ pounds and he seemed considerably improved in color and strength. The appetite was good. The condition of the bowels demanded an occasional cathartic which, however never caused watery stools. Even before discharge on February 18, just three weeks after operation, it was

evident that a marked improvement in the blood picture had occurred, both hemoglobin and red blood cell count being double that obtained on the first admission

After discharge, the improvement continued steadily with greatly increased appetite and strength. The skin lost its sallow hue and became normal in appearance. In the two months since operation the child has enjoyed uninterrupted good health except for one attack of indigestion, the result of overfeeding. Two weeks previous to the last blood count given in the table a rather severe nasal hemorrhage occurred as a result of excoriations. The lowered hemoglobin in the last count is probably to be explained by this hemorrhage.

PATHOLOGIC DESCRIPTION OF THE SPLEEN

The weight is 640 gm, length 18.3 cm, width 10.8 cm, thickness 3.8 at one end increasing to 8.4 at opposite end. The organ is of a uniform bluish-red color. The capsule is for the most part smooth with a few fine adhesions at one pole, where there is also a small circumscribed area (1.5 cm in diameter) of thickening. The vessels of the hilum are normal. No supernumerary spleens are seen.

On section a large amount of dark fluid blood escapes. The cut surface has a uniform smooth glistening appearance of dull red color. The malpighian bodies are distinctly visible but not so large as in the normal spleen. The trabeculae are not prominent. The consistence is increased, it being almost impossible to rupture the spleen by pressure with the thumb. At one end (the larger) of the organ is a distinctly circumscribed, but not encapsulated mass (3.5 cm in diameter), spherical in shape, which shows no malpighian bodies but does present a few minute ochre-colored areas. This area is of the same color and consistence as the rest of the spleen. On section it bulges prominently above the cut surface. The weight of the spleen after escape of fluid blood from three longitudinal incisions is 435 gm.

Gross Diagnosis—Splenomegaly with area of recent infarction.

Microscopic Appearance—Very slight thickening of capsule with no increase of trabeculae. The sinuses are dilated and congested. The reticulum is increased in amount and the cells of pulp appear to be decreased in number. The malpighian bodies show no change except a hyaline thickening of central arteries which is evident in arteries elsewhere. Macrophages are not numerous and deposition of pigment is not seen.

The tumor-like mass described in notes on gross appearance shows intense congestion and hemorrhage without evidence of cell destruction, and represents in all probability the results of occlusion of blood vessels at time of operation.

Histologic Diagnosis—Congestion, increase of reticulum, hyaline degeneration of arteries. (The rather negative histologic appearance is in general that described for splenomegaly with congenital hemolytic jaundice.)

METHODS

The child was kept in a private room of the University Hospital, under the constant supervision of one of us (O H P P) and with a special metabolism nurse in attendance. The complete metabolism study occupied one period of ten days and a supplementary period of five days before splenectomy and a period of ten days after splenec-

TABLE 1—BLOOD EXAMINATION BEFORE AND AFTER SPLENECTOMY

Date	Hb per cent	Erythrocytes	Morphology of Erythrocytes	Reticulated Erythrocytes, Percent age	Resistance to Sodium Chloride Sol		White Blood Cells	Percentage					
					Partial Hemolysis	Complete Hemolysis		Polys	Lymphos	Trans	Monos	Eosinos	Basos
1/13/15*	60	3,820,000	Poikilocytosis, polychromatophilic, occasional normoblasts, anisocytosis	1	0.65	0.425	6,600	41	47		3	7	2
6/1/15*	50	3,150,000	Same as above	61	0.6	0.375	9,600	26	72	1	1		
12/1/15	21	2,020,000	Same as above, no Howell Jolly bodies	9	0.625	0.375	6,100	49	46	3	2		
1/26/15†	33	2,200,000	Same as above		0.65	0.425	6,800	54	43		1	2	
1/24/15 Splenectomy													
2/1/15‡	38	1,570,000	Not noted				16,600	62	32		2	4	
2/11/15‡	45	4,100,000	Morphology much improved, no erythroblasts				15,800	70	22	3	2	2	1
2/15/15‡	45	4,650,000	Same as above				9,000	44	45		10	1	
3/9/15‡	75	4,710,000	Normal in appearance, no Howell Jolly bodies	1	0.525	0.35	14,100	56	27.5	7.5	5	2.5	1.5
4/9/15‡	70	5,070,000	Normal	Occasional	0.525	0.325	11,200	41	43	4	5	6	1

* Count by Dr. I. B. Krumhaar

† Count by Dr. O. H. P. Pepper

‡ Count by Hospital Intern

tomy The first period extended from December 3 to December 14, after which the child went home for the Christmas holidays While at home a supplementary period for the study of uric acid elimination extended from January 20 to January 24 The return to the hospital was delayed on account of the desire of the attendant physicians to improve, if possible, the blood-picture and the general condition On January 28, two days after readmission, the spleen was removed and on Feb 5, after a lapse of eight days, the postsplenectomy metabolism studies were begun and continued for ten days On account of the capricious appetite of the child, it was impossible to adhere to a constant dietary, such as the Folin diet, and therefore considerable liberty was allowed The intake was determined by weighing all foods taken and analyzing portions for nitrogen and fat This policy was followed in both of the ten-day periods, but not in the supplementary five-day period when the child was at home Despite the freedom as to diet, the food intake was quite constant in character from day to day, consisting in the first period essentially of milk, eggs, cereals, apple sauce, bread, crackers, potatoes, butter, sugar, rice and tapioca During the first five days of this period, beef, chicken or fish was allowed once a day, during the second five days, these were entirely eliminated, as they were also in the supplementary period of five days before splenectomy and the ten-day period after splenectomy Thus, except in the first five-day period, the child was on a practically purin and creatin free diet The calorific value of the diet was adequate During Periods I and II (Table 2), the subject received approximately 1,100 calories a day, or about 60 calories per kg or body-weight During Periods IV and V, the subject was on a slightly lower calorific intake, but entirely adequate, namely, 960 calories per day, or about 50 calories per kg of body-weight

The nitrogen of the food was estimated by the Kjeldahl-Gunning method and the fat by Soxhlet extraction The urine was collected in twenty-four hour periods and portions passed during that period were preserved under toluene in an ice-chest The urine was acid to litmus at all times

In the analysis of the urine, the total nitrogen was determined by Kjeldahl-Gunning method, ammonia by Folin's¹ method, urea by Benedict's² method, uric acid by Folin's colorimetric method,³ creatin

1 Folin, O. Eine neue Methode zur Bestimmung des Ammoniaks im Harne, *Ztschr f physiol Chem*, 1902-03, *xxxvii*, 161

2 Benedict, S. R. The Estimation of Urea, *Jour Biol Chem*, 1910-11, *vi*, 405

3 Folin, O., and MacCallum, A. B., Jr. A New Method for the (Colorimetric) Determination of Uric Acid in Urine, *Jour Biol Chem*, 1912-13, *viii*, 361, Folin, O., and Denis, W. On the Colorimetric Determination of Uric Acid in Urine, *Jour Biol Chem*, 1913, *xiv*, 95

and creatinin by Folin's method⁴ and the hydrogen ion concentration according to Henderson's technic⁵

In the study of the feces the fat content was determined by the Folin-Wentworth method,⁶ the iron was estimated by Neumann's method,⁷ nitrogen by the Kjeldahl-Gunning method and urobilin by a slight modification of the method recommended by Wilbur and Addis⁸

Period III (Table 2) was considered a desirable control on account of the high figures for uric acid obtained in the first and second periods. The analyses in this period were, therefore, limited to those determinations of special interest in this connection

In Table 2 are presented the results of the study of nitrogen metabolism

Nitrogen Metabolism—During Periods I and II, before splenectomy, the subject was in a slight plus balance. After splenectomy, during Period IV, a great retention of nitrogen occurred, although the intake varied but little from the previous periods and the subject was not gaining in weight. The logical explanation of this change would be either of the following: (1) reparative processes going on in the body, as indicated by the rapid regeneration of hemoglobin and red cells, or (2) the removal of toxic influences leading to an improvement in the general nutritive condition and thus to the normal retention in a healthy child. The utilization of protein was good at all times. The average percentage of total nitrogen eliminated as urea was 85.5 before splenectomy, and 87.2 afterwards, figures within the normal range. The differences of the averages may possibly be explained by the changes in one of the other nitrogen constituents of the urine, namely, uric acid.

Uric Acid—The uric acid output was exceedingly high in Periods I and II. Period I was not purin free. Period II, however, was practically free from purin intake, notwithstanding which the uric acid output continued on its high level. The urines were highly colored and when allowed to stand gave a precipitate of uric acid crystals. In view of this high elimination of uric acid a supplementary study was made (Period III) during which the subject was again placed

⁴ Folin, O. Approximately Complete Analyses of Thirty "Normal" Urines, *Am Jour Physiol*, 1905, xii, 45.

⁵ Henderson, J. L., and Palmer, W. W. On the Intensity of Urinary Acidity in Normal and Pathological Conditions, *Jour Biol Chem*, 1912-13, xii, 393.

⁶ Folin, O. and Wentworth, A. H. A New Method for the Determination of Fat and Fatty Acids in Feces, *Jour Biol Chem*, 1910 vii, 421.

⁷ Neumann, A. Einfache Veraschungsmethode (Säuregemisch-Veraschung) *Ztschr f physiol Chem* 1902-03 xxxii 114, *ibid*, 1904-05 xliii 32.

⁸ Wilbur, R. L. and Addis, T. Urobilin, Its Clinical Significance, *The Archives Int Med* 1914 xiii 235.

Period	Date	Wt in Kg	Nitro gen Intake, Gm	Urine							Feces, Total Nitro gen, Gm	Total Nitro gen Output, Gm	Nitro gen Bal ance, Gm	Clinical Notes and Temper ature		
				Amt, cc	Sp Gr	Hydro gen Ion Conc *	Total Nitro gen, Gm	Urea, Gm	Am monia, Gm	Uric Acid, Gm					Total Creati nin, Gm	Creati nin, Gm
I	12/ 1/11	17.7	6.45	480	1.022	6.15	6.09	5.25	0.36	0.468	0.476	0.289	0.217	6.63	-0.18	98.2
	12/ 5/11		530	1.018	5.70	5.46	4.53	0.33	0.468	0.308	0.235	0.154	6.00	+3.00	98.4	
	12/ 6/11		480	1.020	5.50	4.99	4.18	0.32	0.468	0.309	0.226	0.096	5.53	-0.37	101.4	
	12/ 7/11		400	1.025	5.85	6.38	5.54	0.26	0.516	0.385	0.270	0.133	6.92	-1.26	99.6	
	12/ 8/11		550	1.019	6.15	6.54	5.60	0.32	0.490	0.405	0.261	0.167	7.08	-0.61	100.2	
	Average		6.55	498	21	5.87	5.89	5.02	0.32	0.482	0.389	0.256	0.153	6.34	+0.12	
II	12/ 9/11	18.2	4.91	280	1.030	6.15	3.96	3.41	0.19	0.410	0.271	0.191	0.093	4.48	+0.43	99.6
	12/10/11		500	1.020	6.30	5.18	4.40	0.31	0.544	0.369	0.239	0.093	5.70	+0.42	100.4	
	12/11/11		270	1.028	6.15	3.00	2.75	0.15	0.544	0.211	0.191	0.023	3.52	+0.60	99.8	
	12/12/11		320	1.026	6.00	4.07	3.43	0.20	0.460	0.271	0.241	0.035	4.59	+0.44	100.2	
	12/13/11		360	1.027	6.00	4.98	4.20	0.24	0.788	0.320	0.270	0.058	5.50	-0.60	98.4	
	Average		5.02	346	26	6.12	4.24	3.61	0.22	0.549	0.288	0.236	0.060	4.76	+0.26	
III	1/20/15			110	1.019		4.59			0.400	0.279	0.225	0.063			
	1/21/15		410	1.020		4.29			0.560	0.270	0.209	0.071				
	1/22/15		415	1.083		3.51			0.620	0.259	0.207	0.060				
	1/23/15		600	1.019		3.81			0.460	0.215	0.215	0.035				
	1/24/15		500	1.024		4.31			0.614	0.300	0.270	0.035				
	Average			491	25		4.10			0.511	0.271	0.225	0.053			

1/28/15

Spleneetomy

IV	2/ 6/15	18.2	7.08	510	1.023	6.00	5.61	4.95	0.22	0.826	0.300	0.203	0.113	5.96	99.6
	2/ 7/15		6.23	590	1.020	6.00	4.71	4.08	0.21	0.294	0.283	0.180	0.119	5.06	99.0
	2/ 8/15		6.41	570	1.020	6.00	4.80	4.16	0.19	0.294	0.311	0.197	0.132	5.15	99.8
	2/ 9/15		4.97	570	1.020	6.70	3.63	3.11	0.12	0.290	0.234	0.176	0.109	3.98	Bronchitis
	2/10/15		4.99	450	1.023	6.80	3.06	2.68	0.10	0.226	0.194	0.176	0.063	3.41	103.2
	Average		5.94	544	21	6.30	4.36	3.80	0.17	0.286	0.264	0.172	0.107	4.71	102.2
V	2/11/15		6.20	630	1.020	5.70	6.15	5.37	0.31	0.206	0.337	0.287	0.098	6.55	99.4
	2/12/15		5.27	320	1.021	5.50	4.83	4.34	0.23	0.272	0.288	0.203	0.041	5.23	98.8
	2/13/15		4.83	530	1.021	6.00	5.64	4.83	0.31	0.320	0.290	0.253	0.043	6.04	Otitis media
	2/14/15		5.38	360	1.032	6.80	4.08	3.54	0.14	0.224	0.238	0.195	0.060	4.48	99.0
	2/15/15		6.17	430	1.025	6.70	4.73	4.13	0.18	0.218	0.248	0.203	0.052	5.13	99.0
	Average		5.57	460	25	6.14	5.09	4.44	0.23	0.266	0.272	0.228	0.049	5.49	

* Expressed as negative logarithms
† Includes preformed creatinin and creatinin as creatinin

on a purin-free dietary, consisting mainly of milk, eggs, shredded wheat and custard. In this period the high output of uric acid, presumably almost entirely endogenous, still persisted. This average (Periods II and III), 0.530 gm of uric acid, is very close to the highest average of uric acid output of an adult on a purin-free diet. Few figures for normal uric acid output in children are to be found in the literature. Closson⁹ in a child of about 7 years of age found an average output of 0.23 gm on a purin-free diet.

After splenectomy the average output of uric acid in Periods IV and V decreased 47 per cent from the average of Periods II and III before splenectomy. It will be remembered that the diets of all these periods were purin free. The appearance of the urine in these later periods was markedly altered, the dark-red color being replaced by a pale yellow, with never a spontaneous precipitate of uric acid.

Hydrogen Ion Concentration—On the same general diet the hydrogen ion concentration of the urine remained constant before and after splenectomy. During Period I, on a mixed diet, an average of 5.87 falls within the average (5.94) of Henderson and Palmer¹⁰. On the purin-free diet yielding a more alkaline ash, the hydrogen concentration before operation is in agreement with that after the operation. It is of interest here to note that the hydrogen concentration is not appreciably altered by changes in uric acid content of urine, although, as shown by Blatherwick¹¹ the ability of a urine to dissolve uric acid is a function of the hydrogen ion concentration.

Ammonia Nitrogen—The ammonia nitrogen in our experiments shows no variations from the normal. Its close agreement with hydrogen ion concentration may be noted, thus a rise in the hydrogen ion concentration is associated with a fall in the ammonia output and vice versa.

Creatinin and Creatin—The creatinin output showed a great constancy in Periods II and III, before splenectomy, on the purin-free diet. During Period I, on a mixed diet, the output is slightly above the average of these periods. During Period IV, after the operation, the creatinin output fell to its lowest point, a decrease of 25 per cent from the average of the other purin-free periods. When the total creatinin, that is preformed creatinin and creatin as creatinin, output of each period is compared, one readily sees that the total creatinin, in all of the periods on creatin-free diet, shows a remarkable constancy.

⁹ Closson, O. E. The Elimination of Creatinin, *Am Jour Physiol*, 1906, vii, 252.

¹⁰ Henderson, L. J., and Palmer, W. W. On the Several Factors of Acid Secretion *Jour Biol Chem*, 1914 xiii, 305.

¹¹ Blatherwick, N. R. The Specific Rôle of Foods in Relation to the Composition of the Urine, *THE ARCHIVES INT MED*, 1914 xiv, 409.

As will be seen from an inspection of the tables, the decrease of creatinin was accompanied by an increase of the creatin amounting to 91 per cent of the average. Why, in Period IV, the partition of creatinin and creatin changed without an appreciable change of total creatinin is difficult to state. During the last two days of this period the patient suffered from a bronchitis with a rise in temperature, but that these are explanatory factors hardly seems plausible.

As regards creatin output, with the exception of the first period, which was not that of a creatin-free diet, the output shows a fair degree of regularity. The increased output in Period IV has already been pointed out.

There is a paucity of data on the creatinin and creatin output of children on controlled diets. The results obtained by Folin¹² on his children offer figures which may serve for comparison.

The great constancy of our total creatinin (including preformed creatinin and creatin as creatinin) output leads us to believe that for the purpose of comparison in children this is the figure to be used rather than the relative or absolute amounts of creatin or creatinin. This point is now under investigation by one of us (S. G.) and will be reported in a later communication. On the basis of this comparison this total creatinin output agrees very well with other published figures for children. The change in the partition of creatin and creatinin will also be the subject of this later paper. We believe our creatin and creatinin figures to be within the range of normal variations.

Fats—The total intake of fats and the separation of fats in the feces are shown in Table 3. In this table Periods I and II represent the presplenectomy and Periods IV and V the postsplenectomy studies. Each period represents five days.

TABLE 3—FAT DETERMINATIONS

Period	Total Intake Gm	Total Output Gm	Per Cent of Fat Utilized	Total Output Fatty Acids Including Soaps, Gm	Per Cent Fatty Acids in Total Fat Output	Total Output Neutral Fats	Per Cent Neutral Fats in Total Fat Output
Before Splenectomy							
I	222	8.88	96.01	6.8	76.8	2.1	23.2
II	223	7.57	96.62	5.1	67.0	2.5	33.0
After Splenectomy							
IV	227	13.56	94.04	10.1	74.4	3.5	25.6
V	269	13.55	94.98	9.8	72.3	3.7	27.7

¹² Folin, O. On Creatinin in the Urine of Children, Jour. Biol. Chem., 1912, 21, 251.

The metabolism of fats shows no abnormal variations. The fat utilization is good, and well within normal limits. As pointed out by Folin and Wentworth,⁹ as total fat increases more of that fat is put out as fatty acids (including soaps).

Iron—Table 4 presents the results of the examination of the feces for iron. As the iron in human urine seldom exceeds 0.001 mg, the urine is not included. Analyses for iron were made on duplicate samples of dried feces representing periods of ten days, before and after splenectomy, respectively.

TABLE 4—IRON ELIMINATION IN FECES

Period	Total Intake Period Mg (calculated)	Total Output Period Mg	Intake per Day Mg	Output per Day Mg
Before Splenectomy I II	37.69	82.99	3.77	8.29
After Splenectomy IV V	45.61	41.11	4.56	4.11

Thus the first ten days correspond to Periods I and II and the second ten days to Periods IV and V. Periods II, IV, and V represent essentially the same diet. The figures for iron intake were calculated from published records¹³ of iron content of foods, hence no claim is made for the extreme accuracy of those figures. They merely serve to show that the iron content of the diet agreed very closely and would not account for the large difference in output. Those differences in output before and after splenectomy amounted to about 40 per cent decrease. That the large output of iron in the period before splenectomy is due to the increased elimination of iron consequent on the excessive destruction of red cells, seems the most plausible explanation. The decreased elimination after splenectomy, with a close agreement of intake and output, show a cutting off of this loss and presumably a return to normal elimination.

Urobilin—Our interest in the urobilin problem has been limited to the influence of the absence of the spleen on the elimination of this substance. In the urine qualitative tests for urobilin gave negative results throughout the experiment. At one time in a concentrated urine a faintly positive reaction was obtained with Ehrlich's reagent. The large bulk of this constituent was in the feces. Because of the small bulk of the child's feces and the necessity of utilizing considerable portions for other determinations, the use of the wet feces for

¹³ Sherman, H. C. Food Products. Macmillan, New York, 1914.

urobilin determination was impracticable. The feces were therefore dried in the usual way and placed immediately in well-stoppered bottles. At the end of the experiment the feces of Periods I and II, before splenectomy, and IV and V, after splenectomy, were combined for urobilin estimation. In view of the previous work⁸ on this substance, it was to be expected that some of the urobilin would be destroyed, or that most of the urobilinogen would be converted into urobilin but whether or not this took place we have no means of determining. The fact remains that considerable urobilinogen was still present at the time of analysis. Inasmuch, however, as both sets of feces were treated alike this was a more or less constant factor. Five gm of feces were extracted with 100 c c of acid alcohol and treated as described in method as outlined by Wilbur and Addis.⁸ The dilution for total mass of feces was then calculated. The dilution follows:

Dilution required for extinction of urobilinogen and urobilin absorption bands: Periods I and II (combined) 71,250, Periods IV and V (combined) 7,954.

These results are in accord with those described by Eppinger,¹⁴ who found, in a variety of clinical conditions accompanied by rapid blood destruction, that the urobilin in the stools sank to normal after splenectomy.

DISCUSSION

The literature concerning the relation of the spleen to metabolism may be considered under five heads: (1) studies both before and after splenectomy for disease of the spleen in man, (2) studies in man after splenectomy, (3) studies of congenital hemolytic jaundice, (4) studies of anemia, (5) studies of the effect of removal of the normal spleen in animals.

1. In only three instances have metabolic studies been made both before and after splenectomy for diseases of the spleen in man. Two of these are Umber's studies of Banti's disease and the third Minot's study of pernicious anemia. Umber studied two individuals splenectomized for Banti's disease and Minot one in whom the spleen was removed as a last resort in pernicious anemia. One of Umber's subjects¹⁴ was a boy of 15 with anemia and icterus. The postoperative period of study covered twelve days and began twenty-four days after the operation. The diet was purin free and a fully controlled metabolic study was made. The results showed no pronounced variation in the distribution of the urinary constituents which could be attributed to the absence of the spleen. Umber makes a point, however, of the fact

¹⁴ Eppinger, H. Zur Pathologie der Milzfunktion, Berl klin Wchnschr, 1913, 1, 1509, 1572.

that after removal of the spleen it was easier to obtain nitrogen equilibrium, attributing the pathologic destruction of protein to a toxic cause. His figures show also a somewhat greater output of purins before the operation than after. In another case of Banti's disease described in this report¹⁵ the "toxic" disturbance of metabolism was not present and splenectomy was not done. In a later study¹⁶ Umber describes a young man of 21 suffering from what he considers as the "toxic" type of Banti's disease. Splenectomy led to striking improvement. The metabolism study of this case was limited to a comparison of total nitrogen intake and output before and after splenectomy. The results confirm his former observation, namely, that a persistent negative balance before splenectomy changes to a positive balance after splenectomy. The postsplenectomy study was made three months after operation. Minot's¹⁷ patient was a colored woman aged 35, on whom metabolic studies were begun fifteen days after splenectomy and transfusion. The figures given for five twenty-four hour periods before and six after splenectomy are not for consecutive days. The examination included total nitrogen in urine and feces and urea and ammonia in the urine. The chief results were a change from a slight negative to a slight positive nitrogen balance and an increase in percentage of urea after splenectomy. The uncertainty of the food intake in the period before splenectomy, the low caloric intake and the shortness of consecutive periods of observation, make these balances of doubtful value.

2. Lo Monaco¹⁸ found in a splenectomized individual no important change in uric acid elimination.

Mendel and Gibson,¹⁹ in the case of a man with enlarged spleen and secondary anemia following malaria, studied the metabolism (total nitrogen, urea, uric acid, ammonia, phosphorus, chlorids and sulphates) after splenectomy, but found no striking variation from the normal distribution of the urinary components. These authors had no pre-splenectomy studies for comparison.

Likewise, Moraczewski,²⁰ who made some studies of both nitrogenous and mineral metabolism in a man of 51, seven months after

15 Umber, F. Zur Pathogenese der "Banti'schen Krankheit" mit besonderer Berücksichtigung des Stoffumsatzes vor und nach der Splenectomie, *Ztschr. f. klin. Med.*, 1904, *lv*, 289.

16 Umber, F. Zur Pathologie der Banti'schen Krankheit. *München med. Wchnschr.*, 1912, *lxix*, 1478.

17 Minot, G. R. Nitrogen Metabolism Before and After Splenectomy in a Case of Pernicious Anemia, *Bull. Johns Hopkins Hospital*, 1914, *xxv*, 338.

18 Lo Monaco, D. Osservazioni sull'escrezione e sulla formazione dell'acido urico nell'organismo, *Bull. d. Soc. Lancis d. ospedali Roma*, 1894, *xiv*, 102. Reference in Schmidt's *Jahrbuch*, 1896 *ccii*, 109.

19 Mendel, L. B., and Gibson, R. B. Observations on Nitrogenous Metabolism in Man After Removal of the Spleen, *Am. Jour. Physiol.*, 1907, *xviii*, 201.

20 Moraczewski, W. Fieberverlauf bei einem Splenectomierten, *Berl. klin. Wchnschr.*, 1903, *xl*, 1002.

splenectomy for "spleen tumor" (malarial), found no important variations. His observations, however, were few in number and were made in the course of an attack of pneumonia which rendered matters of diet and control difficult.

3 The only carefully conducted and complete study of the metabolism in congenital hemolytic icterus is, so far as we are aware, that of McKelvy and Rosenbloom.²¹ The patient, a girl aged 11, on a Folin diet, was studied for six days. The total nitrogen, fat and mineral constituents of the food were determined and both urine and feces studied as to nitrogenous and mineral constituents and the feces as to fat. During a period of six days there was a loss of 4.06 gm of nitrogen, which the authors suggest may be due to a toxogenic destruction of protein. The nitrogen partition of the urine was normal except in the case of the uric acid nitrogen, which was increased. This increase, the writers state, might be due to the increased liberation of nucleoproteins through hemolysis of the erythrocytes. The study of mineral metabolism showed a loss of sulphur, iron, calcium and magnesium and a retention of phosphorus. The fat metabolism was normal. No metabolism studies were made after splenectomy.

In a woman, aged 39, with "chronic family jaundice," Tileston and Griffen²² studied, for three successive days and an added odd day, the output of ammonia, urea, creatin and creatinin on a purin-free and creatin-free diet. They found the elimination of creatinin and urea to be essentially normal, ammonia somewhat high, and uric acid distinctly increased. However, it should be noted that only one determination of uric acid was made.

Haal²³ in a case of family hemolytic jaundice, found an increased excretion of uric acid and of iron.

4 As the changes in metabolism in various types of anemia have recently been summarized by Minot,¹⁷ we will not present this literature in detail. The opposing views are represented by Rosenqvist and von Noorden. Rosenqvist,²⁴ in pernicious anemia and bothriocephalus anemia, found variations in nitrogen elimination, with periods of alternate increased and decreased excretion. In bothriocephalus anemia a well-marked loss of nitrogen while the worm was in the body was

21 McKelvy, J. P., and Rosenbloom, J. Metabolism Study of a Case of Congenital Hemolytic Jaundice with Splenomegaly, *THE ARCHIVES INT. MED.*, 1915, *xv*, 227.

22 Tileston, W., and Griffen, W. A. Chronic Family Jaundice, *Am Jour Med Sc.*, 1910, *cxliix*, 847.

23 Haal. Quoted by Minkowski in *Modern Clinical Medicine, Diseases of the Digestive System*, p. 349.

24 Rosenqvist, E. Ueber den Eiweisstoffwechsel bei der perniciosen Anämie, *Ztschr. f. klin. Med.*, 1903, *xliii*, 193.

followed, after removal of the worm, by a retention. Rosenqvist concluded that in both types of anemia a pathologic decomposition of protein is present. Von Noorden²⁵ opposes this view and as a result of his studies concludes that protein decomposition is not increased as the result of anemia of the ordinary types. The variations in output he believes may be explained by the alimentary and renal disturbances which accompany anemia. That an increased output of nitrogen may occur in anemia due to parasites is admitted, as is also the possibility in non-parasitic anemias of a temporary increase in the output of nitrogen as the result of a sudden destruction of large masses of red cells.

As to uric acid output, von Noorden refers to Rosenqvist's high figures and to other observations and concludes that as a rule in anemia the output is normal but sometimes rises, as in Rosenqvist's work, to twice the normal amount.

It is noteworthy that in bothriocephalus anemia, Rosenqvist found that after removal of the parasite, the purin output increased temporarily and then returned to normal. This temporary increase he explains as due to the regeneration and increased metabolic activity of the blood and somatic cells consequent on the removal of the toxic agent. As the cells recovered their normal equilibrium the output of the purins fell to normal level.

Halpern,²⁶ studying one case of pernicious anemia and one of splenic anemia, found normal values for the various urinary constituents. His figures for purin output are in no way abnormal.

5. The literature of splenectomy in man for conditions other than chronic anemia, as, for example, gunshot wound, rupture, cyst, etc., shows that no metabolism studies have been made in such conditions. Conclusions concerning the effect on metabolism of removal of the normal spleens in the normal individual must, therefore, be based on observations on animals.

Splenectomy in animals (Paton,²⁷ Mendel and Jackson,²⁸ Austin and Ringer,²⁹ Verzar,³⁰ Korenchevski³¹) offers no evidence to show

²⁵ Von Noorden, C. *Metabolism and Practical Medicine*, II, p. 360.

²⁶ Halpern, M. *Zur Frage der Stickstoffvertheilung im Harn in pathologischen Zuständen*, *Ztschr. f. klin. Med.*, 1903, I, 355.

²⁷ Paton, N. *Studies of the Metabolism in the Dog Before and After Removal of the Spleen*, *Jour. Physiol.*, 1900, XXV, 443.

²⁸ Mendel, L. B., and Jackson, H. C. *On Uric Acid Formation After Splenectomy*, *Am. Jour. Physiol.*, 1900, IV, 163.

²⁹ Austin, J. H., and Ringer, A. I. *The Influence of Phlorizin on a Splenectomized Dog*, *Jour. Biol. Chem.*, 1913, XIV, 139.

³⁰ Verzar, F. *Die Grösse der Milzarbeit*, *Biochem. Ztschr.*, 1913, LIII, 69.

³¹ Korenchevski, V. G. *Nitrogenous and Gaseous Metabolism in Splenectomized Animals*, *Russky Vrach*, 1910, IV, 1441.

that the spleen has an important influence on metabolism, though Richet³² states that in order to maintain their weight splenectomized animals require a larger quantity of food than do normal animals. In these experiments the dog, and rarely, the cat, were used.

The literature contains no records of the examination of the feces for fat before and after splenectomy. Tileston and Griffen, in one of their cases of chronic family jaundice, studied, without result, the fats of a single stool. McKelvy and Rosenbloom in their case of congenital hemolytic jaundice report normal fat metabolism.

The literature of iron metabolism is, at best, unsatisfactory, and this is especially true of work on the relation of the spleen to iron metabolism. Most of the work is based on Schmidt's³³ conclusions, drawn from the results of the feeding of iron-poor food to normal mice, that the organism possesses great power of conserving the iron and of re-utilizing it through some form of intermediary metabolism. In this connection Schmidt regards the liver as the depot for iron from the food, and the spleen as the depot for iron from tissue and erythrocyte catabolism.

On the basis of experiments on splenectomized dogs, Asher and his associates (Grossenbacher³⁴ and Zimmermann³⁵) claim to have demonstrated an increased elimination of iron, often double that of normal animals, at various intervals after splenectomy. These studies were made on young puppies and the observations correspond to periods of a few weeks, two months and ten months after splenectomy.

Austin and Pearce³⁶ in a series of five dogs in which the iron elimination was studied before and within two weeks after splenectomy, found a slight increase in iron output in three and practically no change in two. When longer periods had elapsed after splenectomy, as one, nine and twenty months, no evidence was secured of an increase in iron output. Such observations, they concluded, do not support the view that the spleen exerts a constant and important influence on iron metabolism.

32 Richet, C. Des effets de l'ablation de la rate sur la nutrition chez les chiens, *Jour Physiol et d Path gen*, 1912, xiv, 689, *ibid*, 1913, xv, 579.

33 Schmidt, M. B. Ueber die Organe des Eisenstoffwechsels und die Blutbildung bei Eisenmangel, *Verhandl d Deutsch path Gesellsch*, 1912, xvi, 91.

34 Asher, L., and Grossenbacher, H. Beitrage zur Physiologie des Drusen, *Untersuchungen uber die Funktion der Milz*, *Biochem Ztschr*, 1909, xvi, 78.

35 Asher, L., and Zimmermann, R. Beitrage zur Physiologie der Drusen, *Fortgesetzte Beitrage zur Funktion der Milz als Organ des Eisenstoffwechsels*, *Biochem Ztschr*, 1909, xvi, 297.

36 Austin, J. H., and Pearce, R. M. The Relation of the Spleen to Blood Destruction and Regeneration and to Hemolytic Jaundice, XI. The Influence of the Spleen on Iron Metabolism, *Jour Exper Med*, 1914, xx, 122.

No observations in man, on iron elimination before and after splenectomy, are at hand Bayer³⁷ in the study of iron elimination after splenectomy for rupture of the spleen and Banti's disease compared his results with those obtained in normal individuals He found an increased output soon after splenectomy in the case of spleen rupture, but later the elimination returned to normal, in the case of Banti's disease the elimination did not differ from the control McKelvy and Rosenbloom's studies of congenital hemolytic jaundice before splenectomy show that the elimination of iron in this disease is, on the basis of normal figures in the literature, increased This increase they explain as due to the great destruction of red cells

From this brief review of the literature it is evident that in anemia, with or without splenic disease, the majority of investigators have experienced difficulty in obtaining a nitrogen balance Umber^{15, 16} in his study of Banti's disease, Minot,¹⁷ in pernicious anemia, McKelvy and Rosenbloom²¹ in congenital hemolytic icterus, and Rosenqvist²⁴ in pernicious anemia and bothriocephalus anemia all report a pathologic destruction of protein Umber¹⁵ goes so far as to urge this "toxic destruction" as a criterion for operation Von Noorden²⁵ alone opposes this theory of increased destruction of protein in anemia In the case we report, no difficulty was experienced in obtaining a positive nitrogen balance before the operation, feeding was not forced, the patient merely satisfying his natural desires for food Nevertheless, the increased retention after the operation on the same nitrogen intake would appear to support the theory that some toxogenic influence had been removed To this influence, however, must be added as a cause of retention the higher level of reparative processes going on in the body, as, for example, in the bone marrow and possibly other organs The difference between our slight positive balance and Umber's marked negative balance before operation may possibly be a difference dependent on the age of the individuals

Our subject, it will be remembered, was a child, whose natural tendency would be to retain nitrogen for growth, and it is not difficult to imagine that this tendency would affect the toxic destruction to a greater degree than in an adult (The patients in Umber's cases were 15 and 21 years of age)

As regards the elimination of uric acid in anemia, with or without disease of the spleen, one finds the general view to be that the elimination is high Rosenqvist (in 1903) as a result of his studies of

³⁷ Bayer, R. Untersuchungen über den Eisenstoffwechsel nach der Splenectomie, *Mitt a d Grenzgeb d Med u Chir*, 1910, xxi, 335, Weitere Untersuchungen über die Funktionen der Milz, vornemlich ihre Rolle im Eisenstoffwechsel mit besonderer Berücksichtigung des Morbus Banti, *ibid.*, 1913, xxvi, 341

pernicious anemia and bothrioccephalus anemia, reports large outputs of uric acid, sometimes twice the normal amount. He finds that after the removal of the worm in the latter condition, there is first an increased elimination of purins and then a return to the normal. His explanation for this is an increased metabolic activity of the blood and somatic cells following the removal of the toxic agent. In our case, after removal of the spleen, we found the reverse condition, an immediate drop to normal. That an increase took place between the time of operation and the beginning of our first postsplenectomy period (8 days after operation) we cannot say. When, however, one inspects the results of blood examination after operation, it is observed that the increase in red cells and hemoglobin was steady and gradual, no greater during the first eight days after operation than during the subsequent ten days of our metabolism period, so that regenerative processes were at best gradual.

Umber, in his studies, does not report uric acid output, but groups his findings under total purins of which he found, in Banti's disease, a somewhat greater output before operation than after. Haal, in family hemolytic jaundice, found an increased excretion of uric acid. Von Noorden gives as his opinion, based on a review of the literature, that in anemia the output may be normal, but is sometimes increased. Lo Monaco, and Mendel and Gibson report no change in uric acid excretion after splenectomy but present no presplenectomy studies for comparison.

In congenital hemolytic icterus, McKelvy and Rosenbloom report higher uric acid output, but present no studies after splenectomy. They give as an explanation for the increased output, the greater formation of nucleoprotein resulting from the destruction of red cells. Their explanation seems to be inadequate, for it is difficult to imagine the destruction of red cells as being the sole source of this large output of purin. It may, to some extent, be a factor, but the toxic influence on the somatic cells generally, of bile products would appear to be a factor of greater importance. The sallow discoloration of the skin in the disease is indication of the general dissemination of substance absorbed from the bile and our knowledge of the toxic influence of bile constituents offers an explanation for a widespread state of cell degeneration and consequent repair which would readily explain the increased output of products of nuclein metabolism.

Our findings concerning the increased elimination of iron before splenectomy are in practical accord with those of McKelvy and Rosenbloom and can be explained as due to the increased blood destruction. Other comparisons are impossible, as in no study before ours has iron elimination been studied both before and after splenectomy. Bayer's

studies after splenectomy for spleen rupture and Banti's disease do not include presplenectomy studies but comparisons with normal individuals. In his case of Banti's disease the iron elimination after splenectomy did not differ from that of the normal control, in the cases of spleen rupture a slight increased elimination was followed by a return to normal.

The results of our study of urobilin are in accord with the older views as to the source of this substance, that is excessive blood destruction, and also with the views of Eppinger concerning the decrease of urobilin after splenectomy for various diseases of the blood. It is interesting that in this case of acholuric icterus the mass of urobilin was in the feces and not in the urine.

SUMMARY

In a child with congenital hemolytic icterus splenectomy was followed by a disappearance of the discoloration of the skin, a rapid improvement in the condition of the blood and a striking improvement in general health.

Metabolism studies before and after splenectomy gave the following results:

- 1 A slight positive nitrogen balance before splenectomy was followed by an increased retention eight days after operation.

- 2 The output of uric acid showed a decrease of 47 per cent after operation.

- 3 In the period directly after operation a change in the partition of creatinin and creatin elimination occurred; the total creatinin, however, showing but slight change.

- 4 Other urinary nitrogen constituents showed no variations from the normal, and no change was found in the hydrogen ion concentration.

- 5 The utilization of nitrogen was good at all times.

- 6 Fat metabolism was normal.

- 7 There was a large loss of iron through the feces before splenectomy followed by a decided decrease (40 per cent) after operation.

- 8 The excretion of urobilinogen and urobilin in the feces was markedly diminished after splenectomy, the amount after operation was about one-ninth of that excreted before splenectomy.

THE EFFECT OF HEMORRHAGE AND OF OCCLUSION OF THE CAROTID ARTERIES ON VASOMOTOR IRRITABILITY *

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The mechanism which controls blood pressure is one of the most complicated with which the physician has to deal. Arterial pressure depends on two factors—the amount of excitation and the irritability and the resistance to flow in the blood vessels. Peripheral resistance in turn depends to some extent on the elasticity of the arterial walls and the relative viscosity of the blood, but more particularly on the aggregate bore of the terminal arterial channels—the arterioles. This bore is quite variable and depends on several factors. The chemical composition of the blood itself has an important influence on the muscle cells of the vessels. The presence or absence of epinephrin is an example in point. The concentration of carbon dioxide is another factor the importance of which has only lately begun to be realized. The temperature of the blood is probably also of some practical significance. But the most important influence is that exerted by the *vasomotor nervous system* on the muscle cells of the arterioles. This system is essentially an intricate complex of reflex arcs. The term *vasomotor apparatus* is used in this paper to include both the nervous structures proper and the muscle cells to which the nerve impulses are finally delivered.

The activity of the vasomotor apparatus at any given moment depends on two factors—the amount of excitation and the irritability of the various parts of the apparatus. For example, blood pressure may be lowered either by putting the subject at rest, i e, lessening the excitation, or by narcotizing some essential part of the apparatus. Although a great amount of work has been done on the blood pressure as an entity, few attempts have been made to study specifically the influence of different conditions on *vasomotor irritability*. It is altogether likely that a clean-cut knowledge of this matter would aid materially in giving us an understanding of the essential nature of

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surgical shock and sleep as well as various clinical cases of hypertension and hypotension

For some time past the efforts of our laboratory have been directed largely to studies along this line. Particularly, the relation of various ductless glands to vasomotor irritability¹ has been investigated. This paper, which is a continuation of the series, is concerned with the influence of certain circulatory conditions themselves on the vasomotor reactions

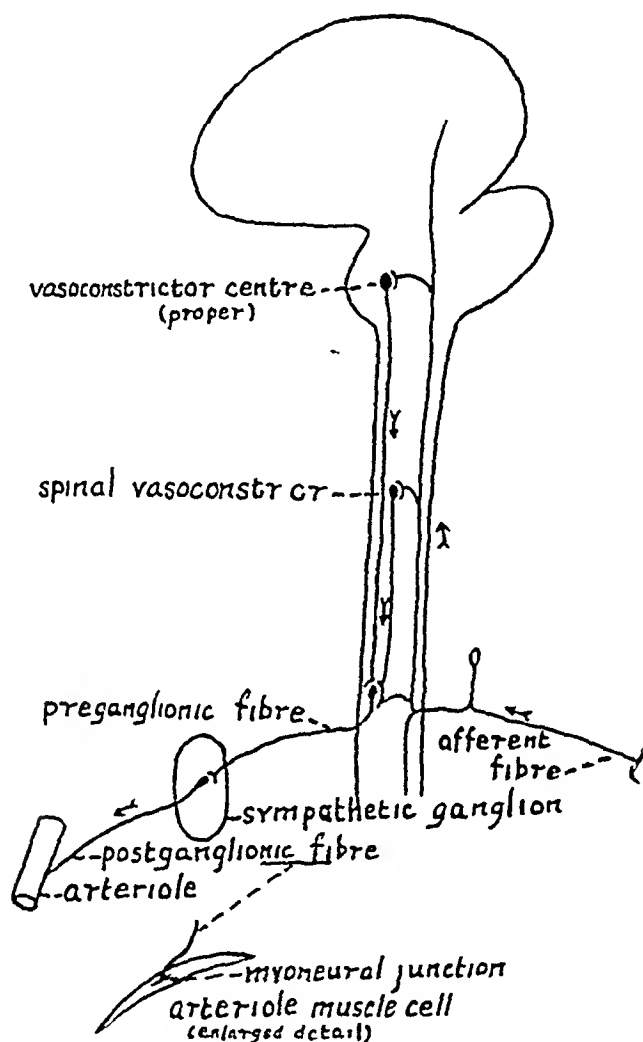


Fig 1—Diagrammatic scheme of the vasomotor apparatus

The accompanying sketch (Fig 1) illustrates the conception of the vasomotor apparatus on which our studies have been based. Although it involves nothing that is new it is included for what it may be worth in adding clearness. Suppose that a given impulse, for instance, one due to a pin prick on the leg, is destined to be delivered to the arteriole walls and cause a rise of blood pressure. The impulse travels over an afferent fiber to the spinal cord. In the cord it may go either upward to the vasoconstrictor center in the medulla or may go directly to a

¹ Hoskins and Wheeler. *Am Jour Physiol* 1914 xxxiv 81 172 263, *ibid*, xxxv 110. Wheeler. *Ibid* 1914 xxxv 283. Hoskins. *Ibid* 1915 xxxvi 423, 424. Rowley. *Ibid*, 1915 xxxvi 471.

subsidiary center in the cord. From here it is relayed to an outgoing *preganglionic fiber* in one of the white *rami communicantes* of the sympathetic system. In one of the sympathetic ganglia it passes over to one or more *postganglionic* fibers, through which it finally reaches the arteriole wall. Between the terminal of this fiber and the smooth muscle cell proper on which the impulse acts is interposed a *myoneural junction*. This consists essentially of a "receptive substance" which bears to the muscle cell somewhat the same relation as does the percussion cap to the gunpowder of a loaded cartridge. Of the various constrictor centers that in the medulla is supposed to be of predominant importance. This is indicated by the fact that cutting the spinal cord just below the medulla usually causes a greater fall of blood pressure than does the further destruction of the cord itself.

This description takes account only of impulses which stimulate the vasoconstrictor mechanisms and cause a rise of pressure. By way of completeness it should be mentioned that other impulses cause a dilatation of the arterioles and a fall of pressure. The details in regard to the vasodilator mechanism are not at all well understood and for the purposes of this paper need not further be considered.

From the fact that curare changes the reflex irritability of the vasomotor system without a corresponding change of blood pressure level, Porter has recently concluded that there are both a vasoreflex center and a vasotonic center.²

The effects of hemorrhage on vasomotor irritability have been studied twice in recent years by American investigators. Porter³ in 1907 and he, with Marks,⁴ in 1908 published two papers on the subject. They were concerned mostly, however, in determining the extent to which blood pressure would have to be reduced before sensory nerve stimulation would cease to be effective in changing blood pressure. It was noted that as the general blood pressure fell a given stimulus produced a smaller absolute change of level than under normal conditions. Porter maintains, however, that the *absolute* change of level is not a proper criterion of vasomotor irritability. He illustrates the matter by an analogy.

An unfaithful trustee robs two women. One of these has \$40,000, the other \$20,000. From each he takes \$10,000. The absolute loss is the same, but while one woman can still live on her income the other must work or beg. It is necessary, then, in measuring vasomotor reflexes to take into account the level of the blood pressure at the beginning of stimulation, and this is done by expressing the change in blood pressure as a percentage of this level.

Judged by this principle the irritability of the vasomotor center is increased by hemorrhage, since the percentile rise of pressure on

2 Porter. Am Jour Physiol, 1915, xxi, 418.

3 Porter. Am Jour Physiol, 1907, x, 399.

4 Porter and Marks. Am Jour Physiol, 1908, xxi, 460.

stimulation is greater Porter's analogy, however, is imperfect so far as hemorrhage is concerned It assumes that the change in conditions during the experiment involves only the center As a matter of fact, however, the conditions throughout the whole vasomotor mechanism are changed We shall revert to this point in a later paragraph Sollmann and Pilcher⁵ on experimental grounds deny the validity of Porter's reasoning They found in experiments involving pressure changes due to aortic compression that as a matter of fact the percentile rise varies *inversely* to the level of pressure According to this finding Porter's and Marks' experiments would indicate a loss of vasomotor irritability during even the earlier stages of hemorrhage Pilcher and Sollmann in a later study⁶ have obtained results which are in direct contradiction to those just referred to. They report that any degree of hemorrhage lessens the pressor response to sciatic stimulation This is true even when the general pressure level remains unaltered In such a case there can be no question of "percentile change"

In view of the conflicting tenor of these late reports the matter seemed to us in need of further investigation, particularly as we were familiar with a somewhat different technic than that previously used An obvious defect in the studies cited is that attention was fixed on the vasoconstrictor center without adequate regard to conditions in other parts of the apparatus

Modern pharmacology, however, has afforded means of studying separately the condition of different parts of the vasomotor mechanism This is done by injecting appropriate drugs which selectively stimulate these parts The condition of the peripheral tissues can be tested by the use of epinephrin which stimulates the myoneural receptive substance, and, according to the best authorities, this only⁷ If there is any question as between the myoneural junction and the muscle cell proper, pituitary extract, which stimulates the cell only, can be used The irritability of the motor cells in the vasoconstrictor centers and the outlying ganglia can be determined by nicotin, which, in proper dosage (0.2 mg.), selectively stimulates these⁸ Dosage in this connection, however, is of great importance If large quantities are used a generalized stimulation of many structures occurs, followed shortly by a paralysis of the sympathetic ganglion cells In this event

⁵ Sollmann and Pilcher Am Jour Physiol 1913, *xxxi*, 211

⁶ Pilcher and Sollmann Am Jour Physiol 1914, *xxxv*, 65

⁷ See, for instance Pilcher and Sollmann Jour Pharm and Exper Therap, 1915, *vi*, 370

⁸ Langley and Dickinson Jour Physiol 1890 *xi*, 297 Pilcher and Sollmann Jour Pharm and Exper Therap, 1915 *vi*, 369

vasomotor impulses are of course completely blocked. Both nicotine and epinephrin, and, to some extent, pituitary extract also, have the advantage that, in the dosages used, they can be repeated several times without significant loss of effectiveness. It is feasible, therefore, to study the changes of irritability of the vasomotor mechanism throughout the course of an experiment.

Using these methods the studies herein reported were carried out. While considerable individual variability was encountered, the essential concordance of the series as a whole permits a brief description of the results. The experiments were all made on unconscious subjects, dogs, either anesthetized with ether or decerebrated. Blood pressure from a femoral artery was recorded by means of an ordinary mercury manometer and float. The use of a Hall reservoir cannula added materially to simplicity of technic. This is a glass cannula of the ordinary arterial type in which is blown a 15 c c bulb (Fig 2). The cannula filled with 10 per cent solution of sodium citrate can be connected by a rubber tube full of the same solution directly to the manometer. One charging of the bulb ordinarily suffices for two hours recording. There is no necessity, therefore, for the cumbersome "positive pres-

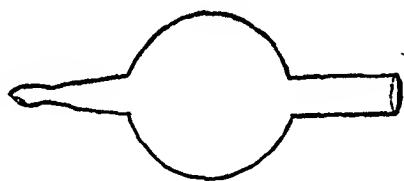


Fig 2—The Hall reservoir cannula, one-half size

sure" and "wash out" arrangements commonly used in such experiments. We have used the method only with dogs. Whether it would be satisfactory with smaller animals we have not ascertained. The rate at which the drugs are injected is an essential factor in quantitative experiments. In order to keep this constant, a flushing system was employed. A large bore cannula was fastened in a femoral vein. It was connected by rubber tubing to a reservoir of 0.8 per cent sodium chlorid solution at an elevation of two feet. The tube was clamped near the end of the cannula. The drug to be given was injected by means of a hypodermic syringe into the tube immediately above the clamp. This was at once released and the drugs instantaneously sent into the blood stream. This technic reduces the margin of experimental error to negligible proportions. Better results are secured in the study of vasomotor reflexes by cutting the vagi and thereby eliminating secondary cardio-inhibitory reflexes. Nearly all our dogs were therefore vagotomized.

THE EFFECTS OF HEMORRHAGE

It was noted that after moderate hemorrhage the reaction to a given dose of nicotine was augmented, often to a striking degree. But the lower blood pressure that also resulted materially changed the mechanical conditions under which the vascular apparatus was working. The individual muscle cells had to contract with lower initial tension, from a shorter initial length and against a decreased load. The results were often correspondingly hard to interpret, although in certain instances the reaction was so greatly augmented as to be unequivocal. More satisfactory results were secured when, after the hemorrhage, enough isotonic saline solution was infused to restore the original pressure level and the reactions immediately determined.

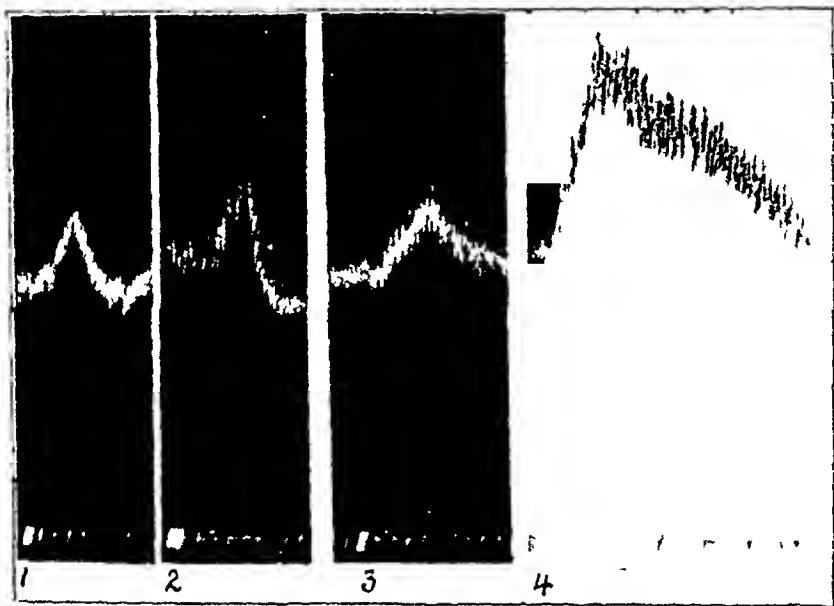


Fig 3—Effect of hemorrhage on vasomotor irritability. Blood pressure from femoral artery. Vagi cut. Graphs 1 and 2, reactions to 1 cc epinephrin (adrenalin), 1:100,000 before and after hemorrhage. Graphs 3 and 4 reactions to 1 cc nicotine 1:4,000 before and after hemorrhage (2 and 4 followed hemorrhage six to eight minutes). Hemorrhage 185 cc compensated with warm saline solution 125 cc. Dog weight, 11 kilos. Base line = 0—pressure, signals and time (five seconds). Reduced to one-half.

The fluid was of course injected at body temperature. Figure 3 illustrates the outcome of such an experiment. Graphs 1 and 2 show the reactions to 1 cc of epinephrin (adrenalin) (1:100,000) before and after hemorrhage. They show that little change had occurred in the condition of the peripheral parts of the apparatus. Graphs 3 and 4 show the reactions to nicotine (1:4,000) also before and after the hemorrhage. The marked augmentation of the reaction shows that the irritability of the vasomotor nerve cells had been increased. Whether the change occurred in the vasoconstrictor center, however, or in the cells of the outlying ganglia can not from such an experiment be deter-

mined It is probable that with the dosage used the rise of blood pressure is due largely to stimulation of the vasoconstrictor center proper, but no definite proof is available No feasible way occurred to us to determine directly in these particular experiments which of the two sites was involved It was supposed, however, that the essential feature of the experiments was an interference with the circulation in the medulla, leading to partial anemia of the center Accordingly the experiments were extended as indicated in the next section

THE EFFECT OF OCCLUDING THE CAROTID ARTERIES

The medulla gets most of its blood supply from two sources, the carotid and the vertebral arteries While clamping the carotids leaves the medullary centers enough circulation to permit their functioning,

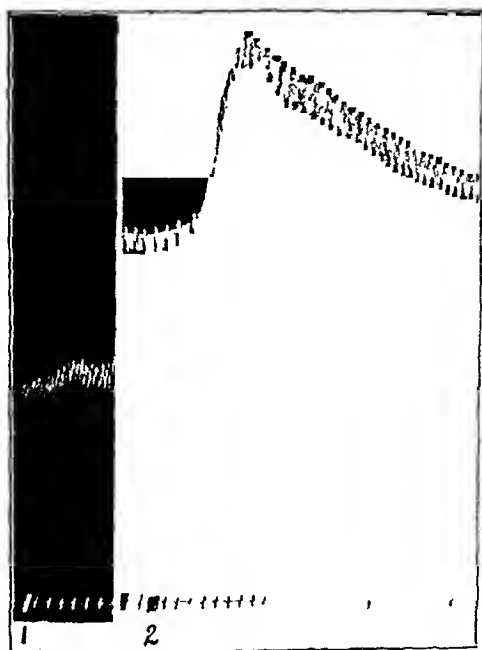


Fig 4—Effect of occluding carotid arteries on vasomotor irritability Blood pressure from femoral artery Vagi cut Graph 1, reaction to nicotine, 1 cc 1 4,000 before occlusion Graph 2, reaction to same dose five minutes after occlusion Base line = 0 — pressure, signals and time (five seconds) Reduce to one-half

it was thought that a sufficient degree of anemia might be caused to produce an appreciable effect In nearly every instance the procedure actually did cause a marked change in the reaction to nicotine Figure 4 illustrates one of the more marked cases Graph 1 shows the reaction of 1 cc of nicotine (1 4,000) Both carotids were then clamped The pressure level rose to the height shown in Graph 2 Five minutes after the occlusion the same dose of nicotine now caused the much greater rise shown in Graph 2 The reactions to epinephrin were prac-

tically the same in both cases. The essential difference, therefore, in the conditions before and after occlusion is an augmented irritability of the vasoconstrictor center. The augmentation in reaction is all the more striking because the occlusion must have partially protected the medulla from the inflow of nicotine. In the few instances in which little augmentation occurred the vertebral arteries probably were adequate to keep up a full blood supply. In one such case pressure on one vertebral artery in addition brought out the augmentation phenomenon. The concordance of both the hemorrhage and occlusion experiments indicates that the augmented irritability was in the vasoconstrictor center proper and not in the outlying ganglia. A characteristic feature of both the hemorrhage and the occlusion experiments was an increase in the length of time the pressor reaction continued.

The occlusion experiments are in harmony with clinical observations. Elevation of blood pressure is one of the accepted signs of increased intracranial pressure following contusions of the brain. But the clinical observations do not, in themselves, show whether the elevated pressure is due to increased irritability of the vasoconstrictor center or to increased stimulation of the center, perhaps by asphyxial products, or to both. The two conditions are allied but by no means identical. That irritability can be greatly augmented without concomitant stimulation is well known to any one familiar with the pharmacology of strychnin. Parenthetically it might be added that "pressure on the medulla" can not, as such, account for the raised blood pressure following brain edema. Slowly developing pressure does not stimulate but depresses.

The underlying feature in all these cases is probably an increase in the hydrogen ions in the cells concerned. Anything which interferes with the circulation of a tissue tends to cause an accumulation of acid products, such as carbon dioxide and lactic acid. This, for example, is probably the essential element in the so-called "hyperemia" treatment (Bier's), which amounts to partial asphyxia and an attendant increase of local tissue activity. A somewhat similar phenomenon is seen in the familiar process of "warming up" of athletes, or, in its laboratory guise, the "stair-case" phenomenon. In each case the efficiency of the mechanism is improved by use. The conventional explanation is that the activity liberates acid products which augment the irritability of the tissues.

The augmented irritability of the vasoconstrictor center described in this paper would seem to have some significance as an adaptive arrangement. Several factors are recognized as aiding in compensation after hemorrhage. Such are the characteristic rapid

heart beat, the passive contraction of the vascular channels due to the inherent elasticity of the vessel walls, and the withdrawal of fluids from the tissue to restore the volume of the circulatory medium. Augmented vasoconstrictor irritability leading to higher vasomotor tonus would cooperate with these other factors in maintaining pressure and keeping up circulation in the brain at the expense of outlying tissues. Similarly when the circulation in the brain is impeded by intracranial pressure the augmented vasomotor tonus by raising systemic pressure aids in keeping the vital centers supplied. This significance of hypertension is of course well recognized.

In this paper only moderate degrees of hemorrhage have been considered (10 to 20 c c per kilo of body weight). As is well known, more extensive loss of blood or serious arrest of its circulation from any cause quickly induces a marked depression of the whole central nervous system. In this depression the vasoconstrictor center of course shares.

SUMMARY AND CONCLUSIONS

1 Certain drugs selectively stimulate different components of the vasomotor apparatus. It is possible by their use to detect changes of irritability in these components.

2 Hemorrhage causes a marked augmentation of the reaction to nicotine but slight or no augmentation of the reaction to epinephrin.

3 Occluding the carotids in most instances leads to similar results.

4 The augmented reactions are probably due, therefore, to increased irritability of the vasoconstrictor center.

5 The phenomenon is probably an adaptive arrangement tending to preserve normal circulatory conditions.

STUDIES IN DIPHTHEROIDS

III BACTERIA ISOLATED FROM ENLARGED GLANDS, ESPECIALLY IN HODGKIN'S DISEASE *

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The object of this paper is to put on record observations on bacteriologic studies in adenopathies, especially Hodgkin's disease, in the light of the findings of Fraenkel, Much, de Negri, Mieremet, Rosenow, Bunting and others

The descriptions given in literature of bacteria isolated from malignant lymphatic granulomas seem to indicate a considerable difference in character among the isolated strains. Early in my work on Hodgkin's disease, it became evident that while diphtheroids might be isolated from many cases of this disease, and indeed from other adenopathies, they varied in morphology and biology. Cultures were sent me by Dr E C Rosenow of Chicago (marked R) and by Dr J A Kolmer (marked K), and comparison of these two sets with those obtained at the Pepper Laboratory showed that the impression stated above was correct. It seemed well to tabulate all the diphtheroids at my command to see if any one form were common in pathologic or clinical Hodgkin's disease or in other adenopathies, and to compare their biology with related organisms. Previous studies with this group have shown the great variations in the biology of morphologically similar diphtheroids, and I did not look for much assistance from this side. Judging from de Negri and Mieremet's work, it seemed that Bordet medium and the morphology, especially in connection with Gram's stain, would enable one to define with some degree of certainty the organism to be considered most important in Hodgkin's disease.

It might be well at this point to state that as Hodgkin's disease I have considered cases with more or less generalized progressive glandular enlargement in which the individual members of the group did not fuse and soften, and showing under the microscope diffuse, mononuclear hyperplasia, prominence of large endothelioid cells and eosinophils, which elements are separated irregularly by a fine fibrosis. These glands should also show small necroses. This description is based on the disease picture as outlined in the work of Reed and

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* From the William Pepper Clinical Laboratory University of Pennsylvania

Longcope Search has always been made for tubercles and tubercle bacilli. The microscopic anatomy of Hodgkin's disease is by no means constant, and I doubt if the borderline between it and that of chronic adenitis and tuberculosis is clear in any one's mind. In citing my own cases below, the name "Hodgkin's disease" has been used only as a clinical term, pathologic diagnosis being made on the anatomic findings. The material for these studies was obtained by operation under local anesthesia or gas. In the arthritis cases, the most accessible gland or that near the principal joint focus was removed. Free glands of moderate size and firmness were selected from the Hodgkin's cases.

The following is the method used in studying the cases.

A section of a gland removed at operation was cut at once, one piece put into Orth's fluid or liquor formaldehydi, another dropped into hot oil, transferred to ether, then into salt solution and from that into a large sterile bottle, cut up with scissors within the bottle, pieces removed and planted on Bordet medium tubes and plates, serum dextrose agar, Loeffler's blood serum, serum water and rabbit blood agar. Smears made from a bit of the gland stained with Loeffler's, Gram's, carbolfuchsin and Wright's. In most of the cases the bits of tissue remaining after inoculating sufficient culture mediums were put into 15 per cent antiformin, incubated at 37 C over night and seeded on the same mediums. Two of the cases were fortunately exposed to antiformin only for an hour because cultures were positive then and negative after eighteen hours' exposure. All the cultures were plated on Bordet medium except two early ones before the necessity of this procedure was appreciated. It is necessary in this work to be sure that one has pure cultures. It is best to plate on Bordet medium and fish after three days' incubation, at which time the slightly varying colonies are differentiated. This medium has a good contrast surface.

The accompanying table was compiled from records made on cultures growing on mediums of the same method of preparation, and the cultures from Drs. Rosenow and Kolmer were tested on the same batch of mediums and at the same time, as Nos. 8772, 8916, 9144, 9265 and 9392, while the control, true diphtheria bacilli and pseudo forms 873-1 and 873-3 were grown on the same batch of culture material as 6638 and 6640. Observations on carbohydrates were made on litmus agar sugar mediums of reaction neutral to phenolphthalein. The other standard mediums were of 1+ reaction. Cultures isolated in the Pepper Laboratory are given numbers, while those from Drs. Rosenow and Kolmer are lettered. The generations from which these notes were made varied from the third to the tenth. Nos. 8772, 8916, 9265, 9144, 9392, the R's and the K's were all passed through three times and remained uniform in biology. The morphology has not been controlled by repetition to the same extent, but comparison of the original smears and those made during the cultural observations indicate that the staining characters remain the same. Culture 8772, now in its thirty-third generation, is the only one to change materially, having lost its beaded and segmented character and staining as long, slender, solid

rods The drawings were made by the same person with the same equipment throughout

CASE 1 (6638) —A S, a woman, aged 22, three months ago noticed that her neck began to swell on the left side, giving her no discomfort or pain About two weeks later she noticed the same condition on the right side One month later she noticed that she had lumps in the right axilla There never was any pain or discomfort in these swollen glands The glands on both sides of the neck have been steadily increasing in size, the most rapid growth shows in the glands in the right axilla

Physical examination reveals a large mass of glands in the anterior of the neck on both sides On the right the nodules are more discrete, although a number of them are massed together, on the left side they are at places definitely outlined, but the majority of the mass of glands are adherent They are all very hard, smooth and noninflammatory, and in places are fixed quite tight In the right axilla are a number of glands, one about the size of an egg, which is hard, smooth and discrete It is also noninflammatory Blood R B C, 3,350,000, W B C, 14,200, Hb, 53 per cent, P, 81 per cent, L, 14 per cent, M, 3 per cent, T, 2 per cent, E, 0 per cent The axillary gland was removed under local anesthesia

Section shows chronic lymph granuloma with an attempt to preserve lymphoid collections, but these and the chords are encroached on by diffuse round cell and endothelial leukocyte infiltrates and fine fibrosis Eosinophils and multinucleated cells are numerous Connective tissue is everywhere increased and hyaline The focal necroses are missing, growth is active, as indicated by normal mitosis and many compression giant cells Diagnosis, lymph granuloma

CASE 2 (6640) —L P, aged 30 The patient first noticed a swelling in the right side of the neck one year ago Twelve weeks ago cough and vomiting were present, eight weeks ago, fever, pain in abdomen, and sweating occurred

Physical examination showed the lymphatic glands of the neck, axilla and right inguinal region to be greatly enlarged, the greatest enlargement was in the right cervical chains, here some were the size of small lemons, they extended from the angle of the jaw to the clavicle There was one large one in the right submaxillary region The enlargement was not so marked on the left, in the axillae they were about the size of horse chestnuts, they were not so large in the right groin, small ones were found in the left groin No glands were palpable in the popliteal space or in the epitrochlear region The glands were soft, movable, discrete and unattached to the skin, not tender The chest showed pleural effusion, the abdomen, ascites, palpable liver and palpable spleen Blood Hb, 40 per cent, R B C, 3,290,000, W B C, 4,100 Von Pirquet negative Urine Albumin and casts

Section shows a tissue made up of large lymphocytes or endothelioid cells with a ground work of fine fibrosis and many scattered polynuclear cells Eosinophils are numerous There are many areas of necrosis, some wholly hyaline, others with a core of chromatin debris surrounded by a hyaline necrosis Giant cells and multinucleated cells are numerous, most of which seem to be compression giant cells

CASE 3 (8916) —W P Two years ago the glands on the left side of neck began to swell followed shortly by the left submaxillary gland Previous to this for some time he had had enlarged glands or kernels in his neck, especially over the left mastoid About a year ago a playmate of the patient died of Hodgkin's disease, which started in a similar manner to that of the patient The blood count showed Hb 85 per cent R B C, 4,330,000, W B C, 5,500, 19,7, P 15 per cent L, 38½ per cent L M 41 per cent, E, 4 per cent, T 1 per cent The group of large mononuclears here includes large cells with pale cytoplasm and large mononuclears and transitionals

ILLUSTRATING FIGURES 1-4

Fig 1—1, 6638*a*, 48 hours agar—Loeffler, 2, 6638*a*, 48 hours Bordet—Loeffler, 3, 6638*b*, 48 hours agar—Loeffler, 4, 6638*b*, 48 hours Bordet—Loeffler, 5, 6640, 48 hours agar—Loeffler, 6, 6640, 48 hours Bordet—Loeffler, 7, 8916-1, 72 hours agar—Loeffler, 8, 8916-1, 72 hours Bordet—Loeffler, 9, 8916-1, 72 hours blood serum—Loeffler, 10, 8916-1, 72 hours agar—Gram, 11, 8916-2, 48 hours agar—Loeffler, 12, 8916-2, 48 hours blood serum—Loeffler, 13, 8916-2, 24 hours agar—Gram, 14, 8916-2, 24 hours Bordet—Gram, 15, 8916-4, 48 hours agar—Loeffler

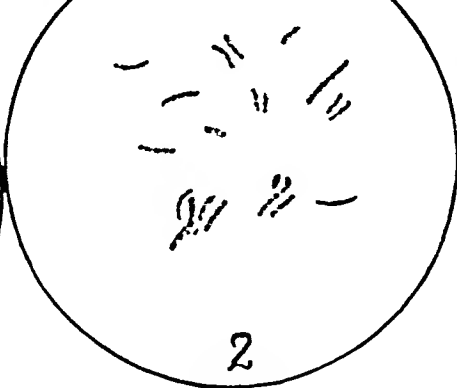
Fig 2—16, 8916-4, 48 hours Bordet—Loeffler; 17, 8916-4, 48 hours blood serum—Loeffler, 18, 8916-7, 48 hours agar—Loeffler, 19, 8916-7, 48 hours Bordet—Loeffler, 20, 8916-7, 48 hours bouillon—Loeffler, 21, 8916-9, 72 hours bouillon—Loeffler, 22, 8916-9, 72 hours Bordet—Gram, 23, 8916-10, 72 hours Bordet—Gram, 24, 9265, 48 hours blood serum—Gram, 25, 8772, 48 hours agar—Loeffler, 26, 8772, 72 hours blood serum—Loeffler, 27, 8772, 48 hours agar—Loeffler, 28, 8772, 72 hours Bordet—Gram, 29, 8772, 72 hours blood serum—Gram, 30, 9144-1, 48 hours Bordet—Gram

Fig 3—31, 9144-2, 48 hours blood serum—Gram, 32, 9392-1, 48 hours agar—Loeffler, 33, 9392-1, 48 hours Bordet—Loeffler, 34, 9392-1, eighth day Bordet—Loeffler, 35, 9392-1, 72 hours Bordet—Gram, 36, R A-1, 48 hours Bordet—Loeffler, 37, R A-2, 48 hours Bordet—Loeffler, 38, R B-1, 48 hours Bordet—Gram, 39, R B-2, 48 hours Bordet—Loeffler, 40, R B-2, 72 hours Bordet—Gram, 41, R B-4, 24 hours agar—Loeffler, 42, R B-4, 48 hours Bordet—Loeffler, 43, R B-4, 48 hours Bordet—Gram, 44, R C-2, 24 hours agar—Gram, 45, R C-3, 24 hours agar—Gram

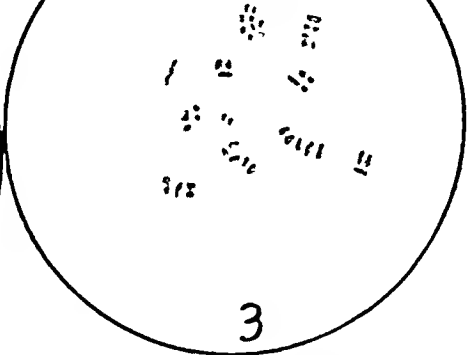
Fig 4—46, R C-3, 24 hours Bordet—Gram, 47, R C-3, eighth day blood serum—Gram, 48, R D-1, 48 hours bouillon—Loeffler, 49, R D-2, eighth day agar—Gram, 50, R E-1, 72 hours Bordet—Loeffler, 51, R E-1, eighth day agar—Gram, 52, K I-1, 72 hours blood serum—Loeffler, 53, K II-1, 48 hours Bordet—Gram, 54, K II-3, 72 hours Bordet—Gram, 55, K II-4, 48 hours Bordet—Gram, 56, Klebs-Loeffler "K," 48 hours agar—Loeffler, 57, Klebs-Loeffler "K," 48 hours Bordet—Loeffler, 58, Klebs-Loeffler "K," 24 hours blood serum—Loeffler, 59, 873-1, Pseudo-diphtheria 48 hours Bordet—Loeffler, 60, 873-3, Pseudo-diphtheria 48 hours Bordet—Loeffler



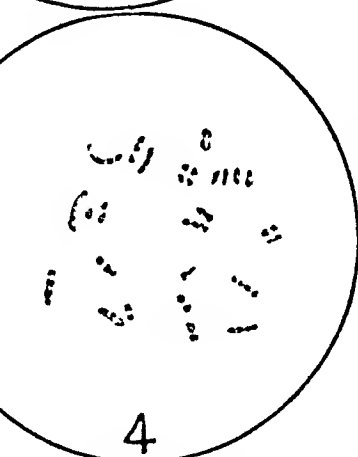
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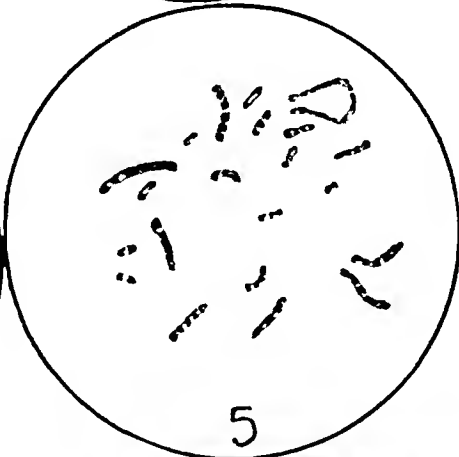
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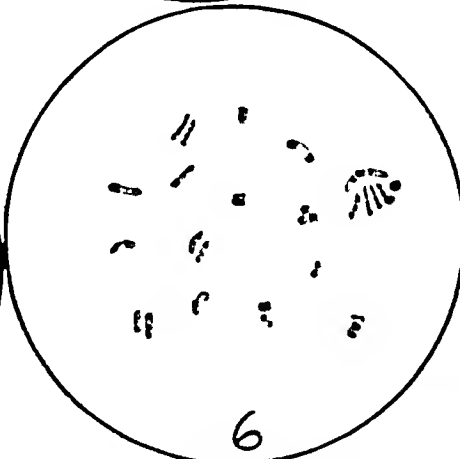
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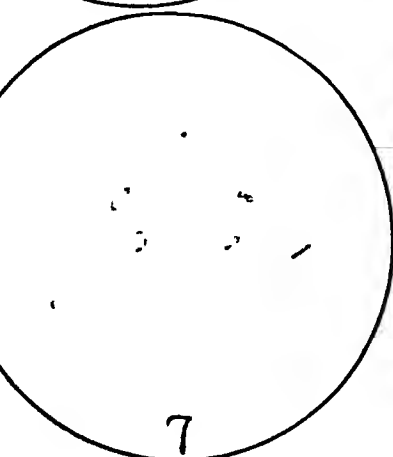
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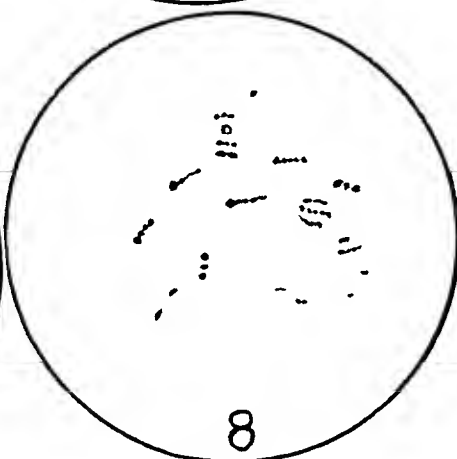
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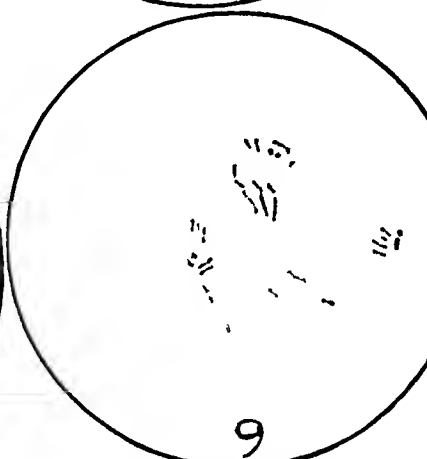
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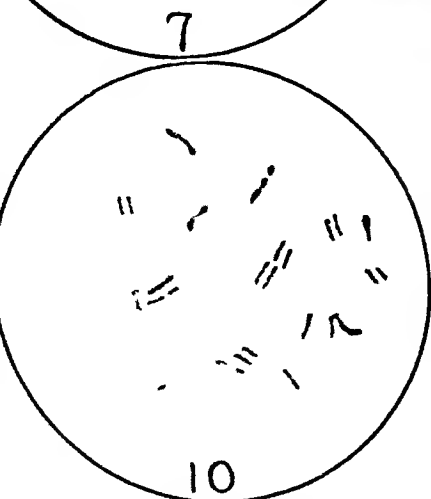
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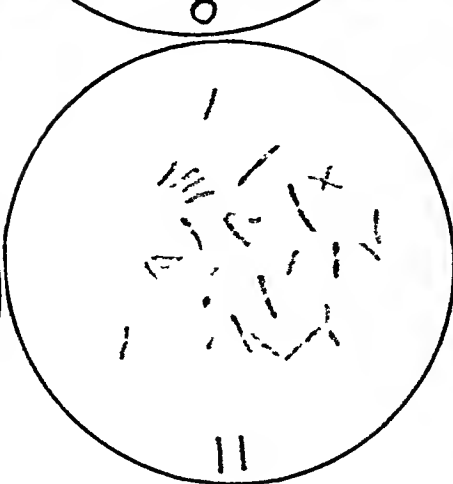
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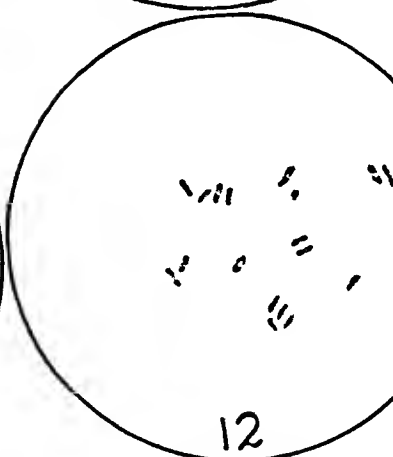
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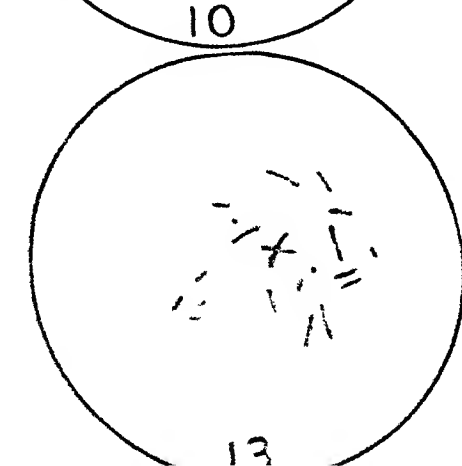
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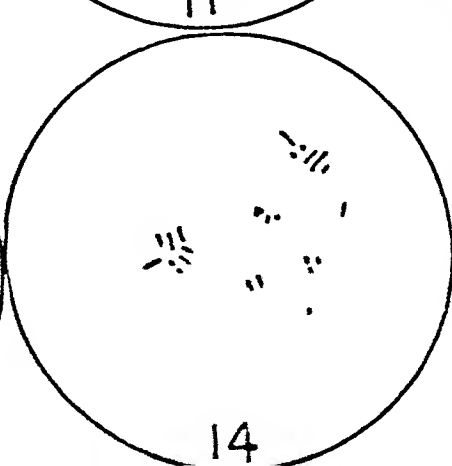
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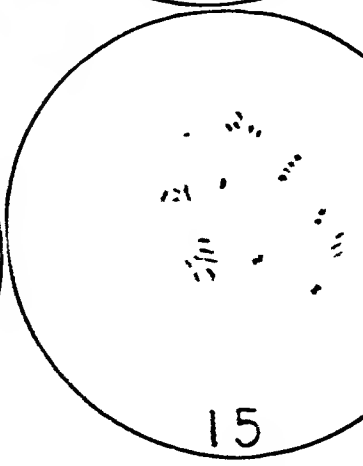
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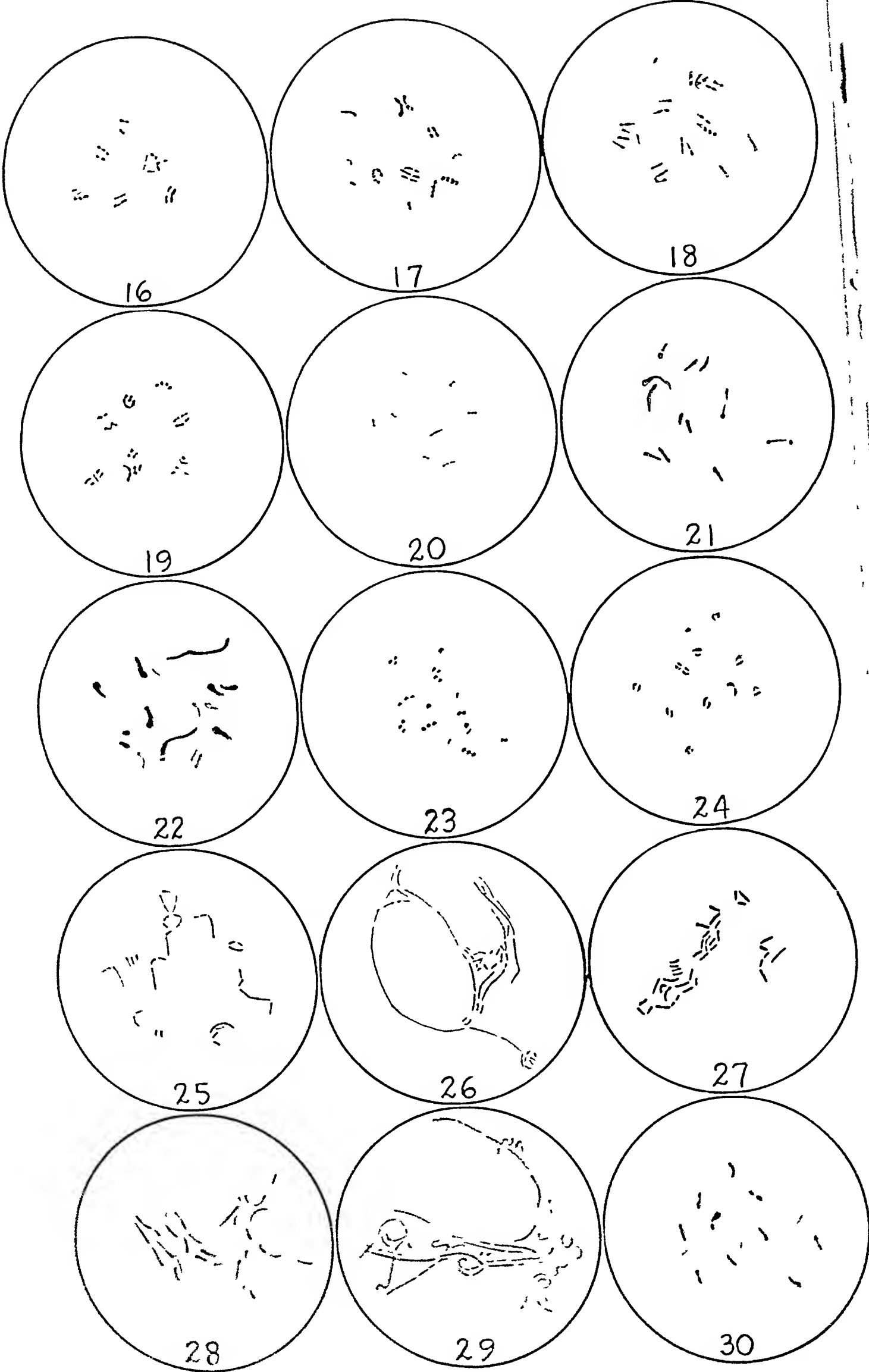
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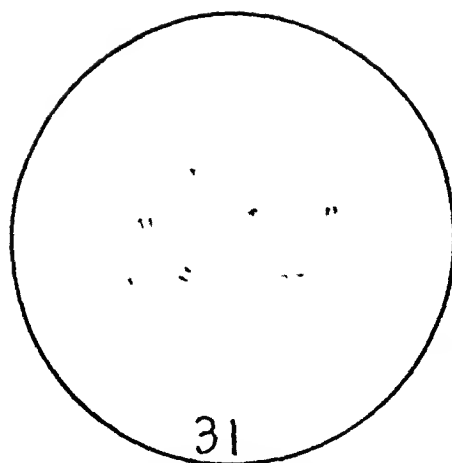


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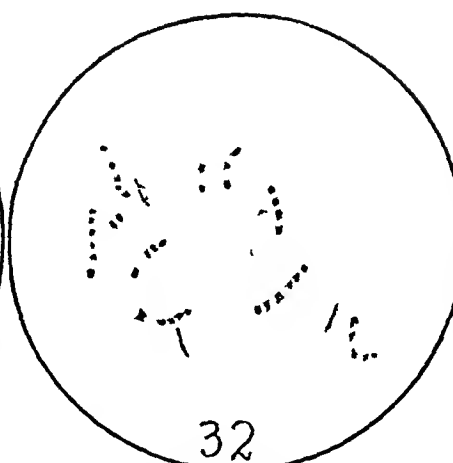


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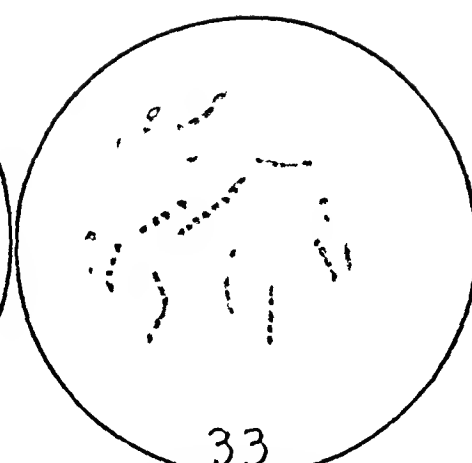




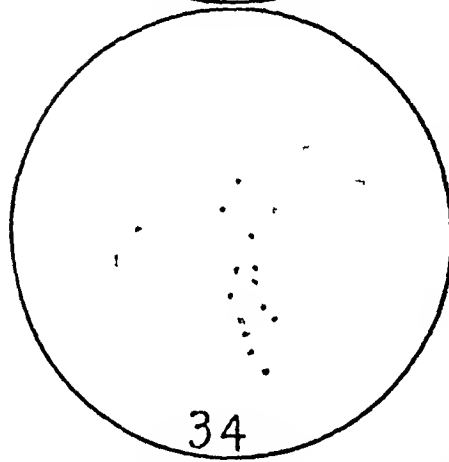
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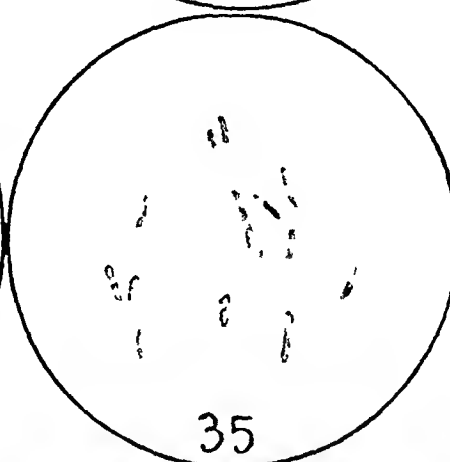
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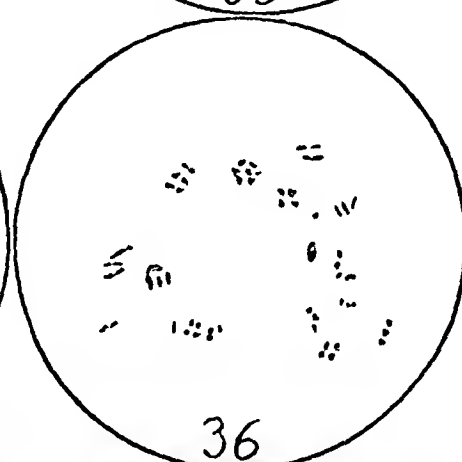
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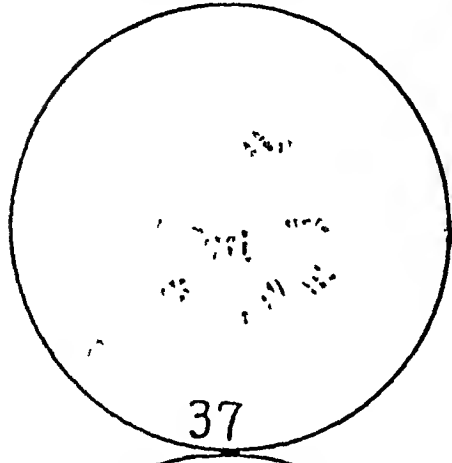
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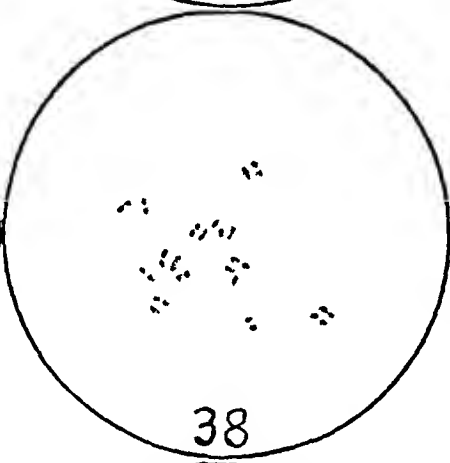
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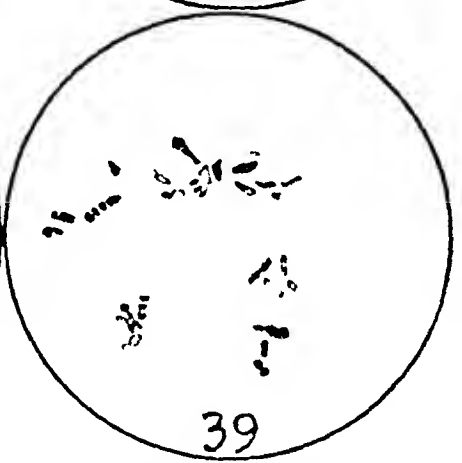
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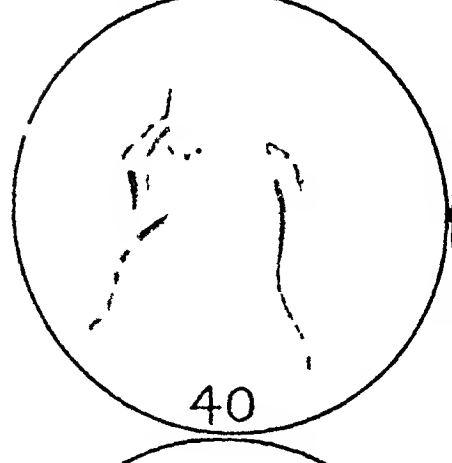
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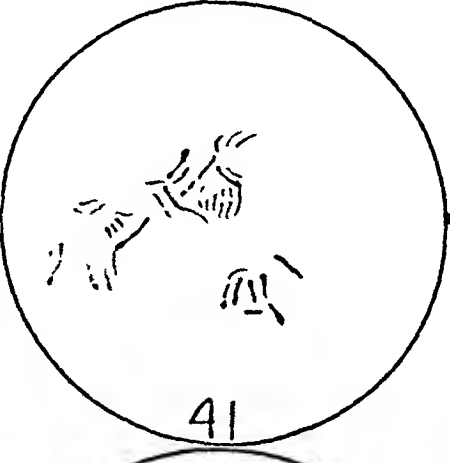
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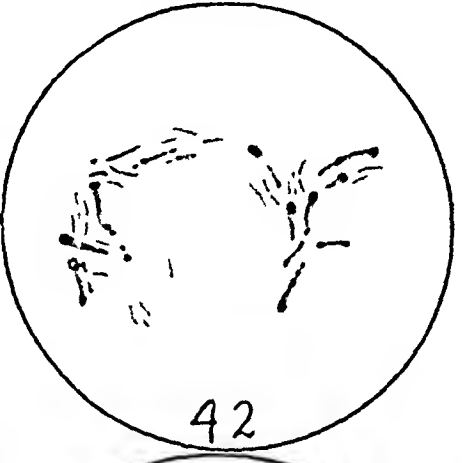
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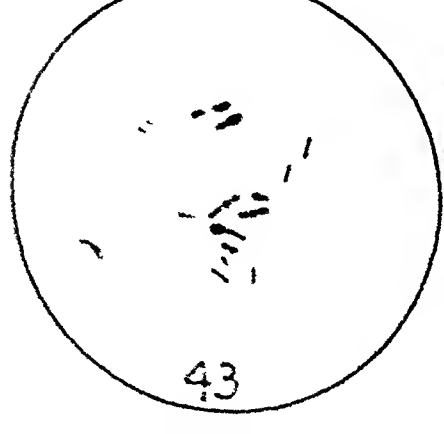
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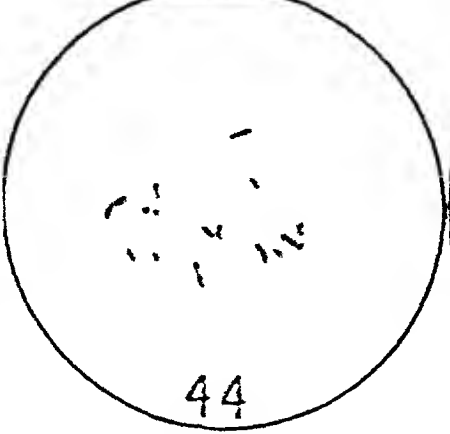
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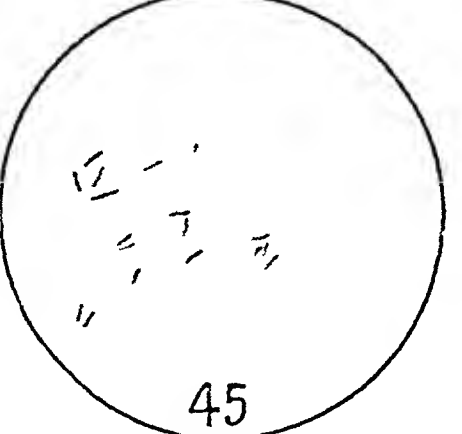
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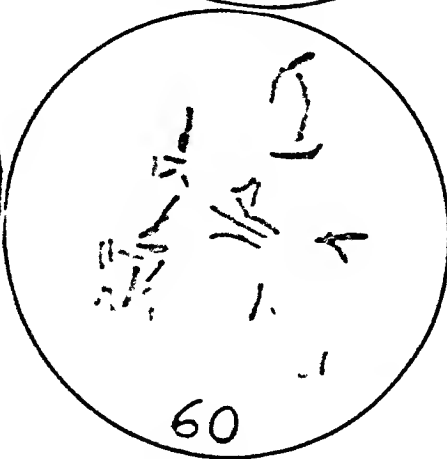
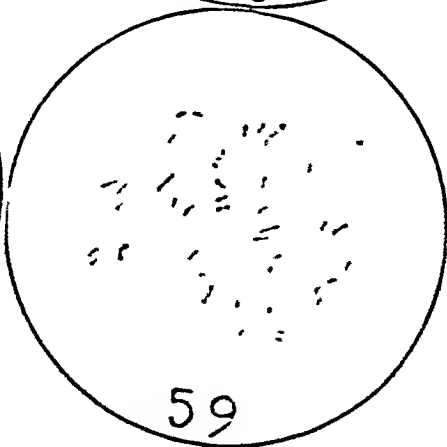
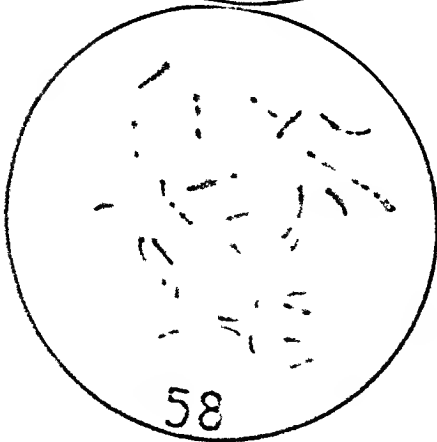
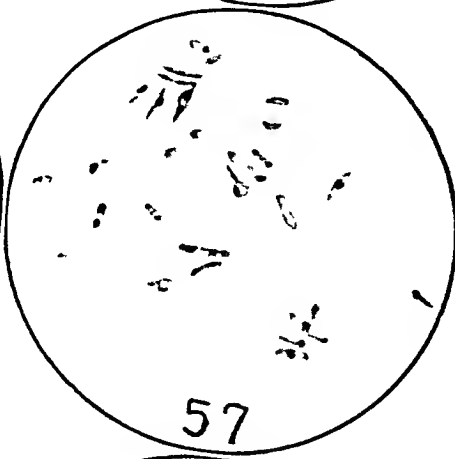
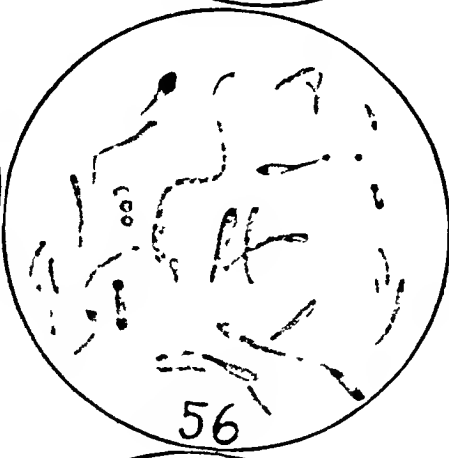
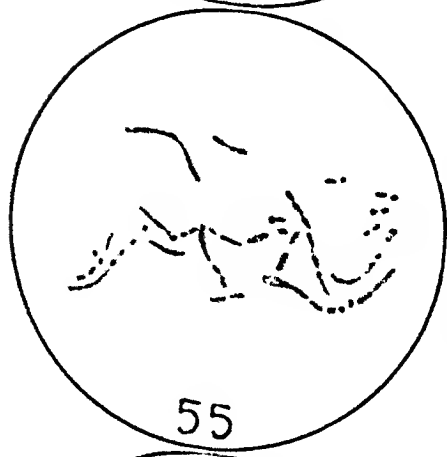
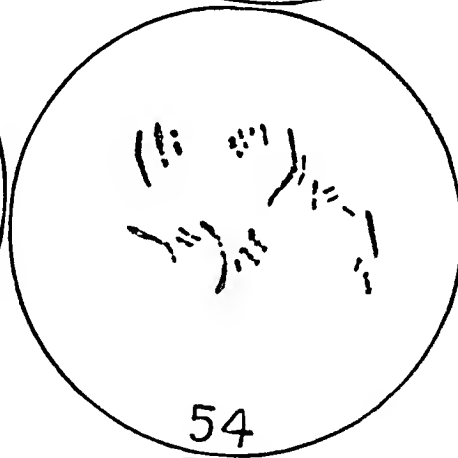
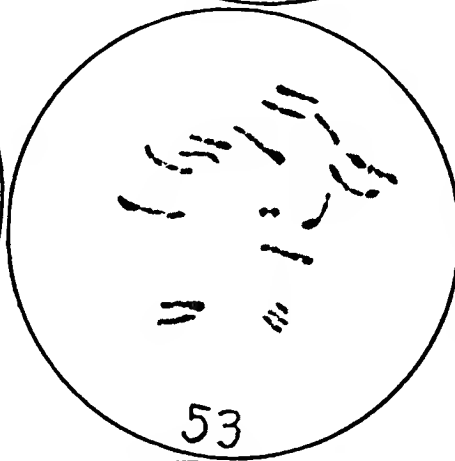
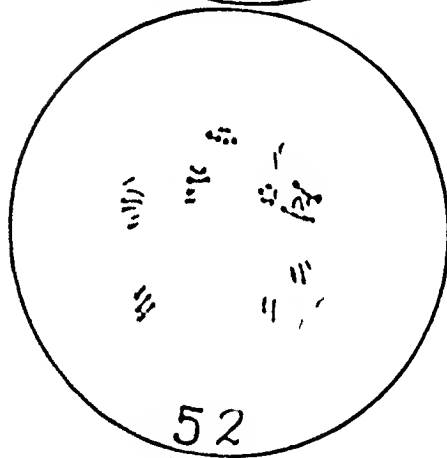
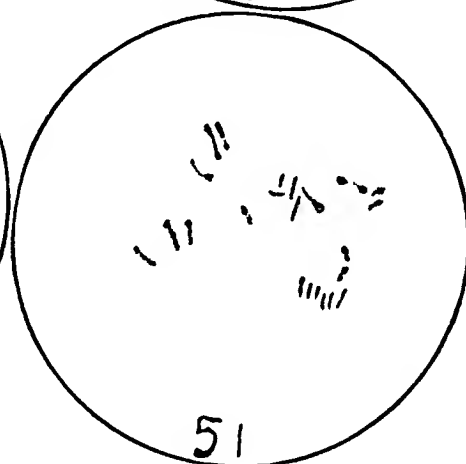
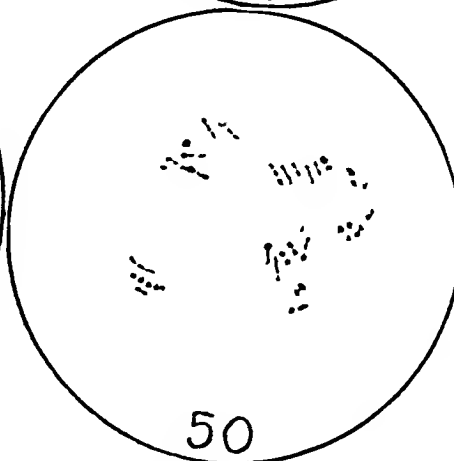
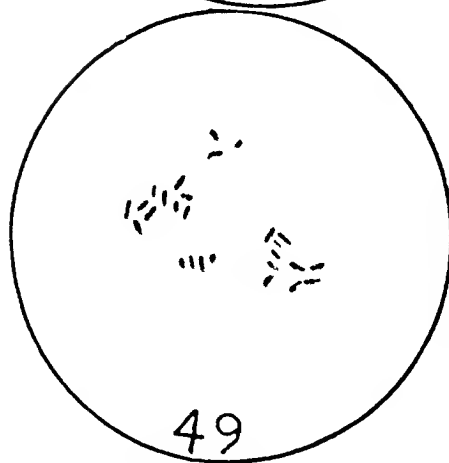
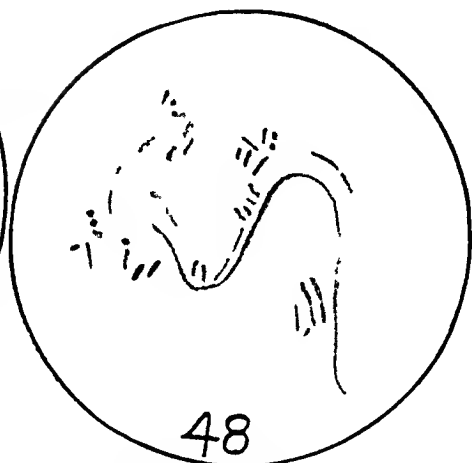
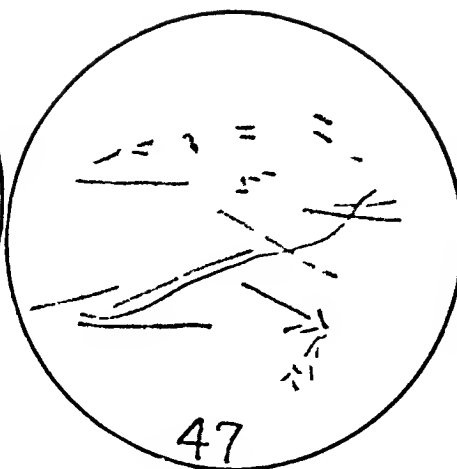
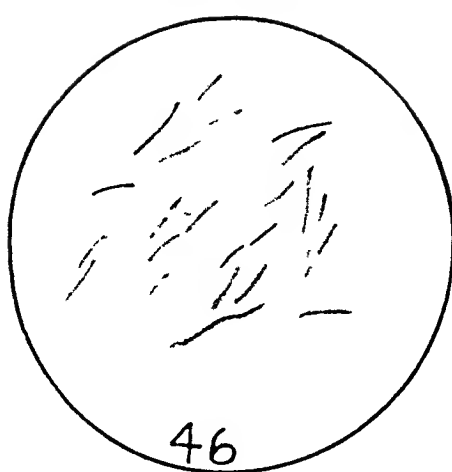
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Physical examination showed the patient to be sallow or ashy. His neck was thin and suggested loss of weight. Considerable swelling was present in the left side of the neck involving the glands below the angle of the jaw and cervical region and postoccipital, but numerous small glands could be felt on both sides of the neck from the clavicle upward. There was doubtful enlargement in the right axilla, none in left. The inguinal glands were more distinct. A possible slight dulness was noted at the root of the right lung and harshness of inspiration. The sounds, however, were not altogether certain. The spleen was doubtfully palpable. No abdominal masses were noted.

Nov 4, 1913. Marked improvement has appeared in the condition of the glands. Those of the neck have almost disappeared, one is still palpable just above the clavicle, none are discoverable in the axilla.

March 21, 1914. Some enlargement of the cervical glands still exists. These seem to be variable in size. A little while ago the patient noticed an enlarged gland in the right forearm or epitrochlear region, but this has disappeared.

March 28, 1914. Blood examination to-day shows a little improvement in hemoglobin and red cell count. Two series of Roentgen ray treatments have resulted in considerable improvement.

A gland about 5 by 4 mm. over the tip of the mastoid was removed under local anesthesia. The smears failed to show any rods. A section showed fairly well-encapsulated tissue of the general outline of a lymph node consisting of a disturbed follicular border and a medulla composed chiefly of fibrous tissue containing many dilated blood channels whose walls are imperfect and the endothelium of which is scanty. The follicular border shows loosely arranged lymphoid cells between which are red blood cells, and in the larger hyperplastic follicles, cells of the large mononuclear series. The endothelium of sinuses cannot be said to be increased. There are practically no eosinophils. There are no large phagocytes, no giant or ring cells. Here and there a fair number of polymorphs may be seen. The connective tissue of the medulla is well formed. The fibrils are clear and there seems to be no degenerative change in the section anywhere. It seems more like a chronic lymphadenitis than Hodgkin's disease or tumor.

The patient was continued on Roentgen ray and vaccine treatment and improvement has continued.

CASE 4 (9265).—E. P., aged 24, colored, has had general adenopathy and rheumatic pains throughout the joints and extremities, for only about four weeks. The gland remained firm and discrete and the case seemed one of Hodgkin's disease. Histologic section showed chronic follicular enlargement with obliteration, a notable increase in large mononuclears and fibroblasts of chords. Eosinophils and necrosis are absent, there was no tubercle formation, no giant cells. Cultivation produced a large micrococcus in pairs, each individual having a long transverse diameter but no rods. The patient refused to stay in the hospital and was lost to further observation.

CASE 5 (3541).—McC. had adenopathy of both cervical and right axillary regions which began as an enlargement of the right epitrochlear gland. The right pectoral region was indurated like carcinoma *en cuirasse*. After removal of some glands for experimental purposes, the patient developed a general pneumococcus infection and died.

Section from operated glands showed a chronic adenitis with features of sarcoma, in places very like endothelioma. The cultures remained sterile except on a Bordet medium tube and one blood agar tube and one blood serum tube on which grew a white coagul. No colonies of rods could be discovered.

Necropsy showed a sarcomatous growth of the lymph glands probably endothelioma. As the cell was small, round or oblong with a small amount of acidophilic protoplasm and a large vesicular and a perichromatic nucleus, the tumor possibly arose from the endothelial cells of the lymph spaces. The rest

of the postmortem indicated arteriosclerosis, fibrosis in the lung and the evidences were found of the acute infection through which the patient had passed

CASE 6 (8772) —L W, a woman, aged 32, had bilateral cervical adenopathy of four months' duration with firm, discrete glands. At operation those removed showed a yellow-gray surface with a few minute points of hemorrhage. Near the margins there was apparently fine fibrosis. The gland section was dry. Microscopic examination revealed a rapidly growing lesion chiefly along the lymph channels, made up of large, palely staining, irregular cells, probably endothelioma. The fibrous tissue was abundant, but loose. There was no resemblance to Hodgkin's disease. Culture on Bordet and blood agar gave some colonies of cocci and one brownish colony on a Bordet tube, proving to be an irregular granular rod.

Roentgen ray and vaccine treatment was instituted with at first favorable results. The patient was pregnant on arrival at the hospital, and it was decided that termination of this condition was necessary for her good. After return from the maternity, treatment for the adenopathy was resumed. The patient left the hospital in a short time. The report is that she has died.

CASE 7 (8604) —J, aged 19, had bilateral adenopathy with an acute exacerbation since the removal of adenoids and tonsils two months before operation. Large masses of discrete glands were found, the individual glands being soft and resilient. Operation showed soft, fatty, necrotic, gray-yellow glands with here and there caseous necrosis. Caseous tuberculosis was confirmed by stain and section. *M. albus* appeared in pure culture in every tube. No diphtheroids were noted.

CASE 8 —A G F, a woman, aged 33, was in good health until seven years ago, when she became pregnant and at the same time developed a swelling in the right side of the neck which lasted two months and then disappeared. After the birth of her child, a similar swelling developed in the right axilla which remained until five years ago when it was drained, at which time it was very much inflamed and contained pus. Two years ago glands were removed from the neck and axilla.

Smears and cultures made in the ordinary way showed no tubercle bacilli, two slender, solidly staining rods and one pair of cocci by Loeffler's stain. The small lymphocytes, large mononuclears and a few polynuclears were most numerous. Incubation of the gland on Bordet and blood agar for six days showed nothing. A section from the gland showed a disturbed follicular border, between the lymph-cell collections of which are irregular areas of epithelioid cells and an occasional giant cell. The margins of the epithelioid cell collections showed numerous fibroblasts toward the center of the gland. Areas of eosin-staining necrosis are present. No eosinophils are to be seen. A few tubercle bacilli may be noted.

CASE 9 (9144) —M W, a white woman, aged 22, had always been healthy until four months before admission, when she had an attack of tonsillitis lasting one week. Following this her left wrist became swollen, red, hot, tender and stiff, and later her left ankle, right wrist, knees, elbows and shoulders became involved in a similar manner. Finally the finger joints were involved and these were at the time of admission, giving her the most trouble. In the meantime she had been given twenty-four antirheumatic antitoxin injections without benefit, and, indeed, had lost 18 pounds in weight.

Physical examination showed a somewhat sallow complexion, a gland the size of a finger tip was palpable in the right axilla, and a few posterior and anterior cervical nodes were palpable. The tonsils and pharynx were somewhat congested. There were sordes on the teeth and a slight pyorrhea was present. The elbows were fixed in partial flexion, the wrists limited in motion. The proximal phalangeal joints of both hands were swollen, slightly reddened, hot and tender, these swellings were fusiform in shape. The power in the hands was decidedly diminished. The gonococcus fixation test and Wassermann were

negative. Roentgenoscopy of the hands showed beginning atrophic arthritis of the proximal phalangeal joints. May 21, Dr Eliason removed a gland from the right axilla for culture and microscopic examination. On discharge she was greatly improved, the elbows were movable, the swelling of ankles and wrists had diminished, the power in the hands had increased.

A smear failed to show any bacteria. Cytology was negative. A section shows large loose follicles with quite definite increase in delicate connective tissue. The interfollicular sinus architecture is disturbed by the growth of the follicles, and fibrous tissue is definitely increased. The capsule is little, if any thickened. No especial kind of cell other than the small lymphoids is present. There is no necrosis, no eosinophils.

CASE 10 (9392) —J M, a woman, aged 41. Her present illness began seven years ago, coming on a few hours after delivery with pain and tenderness in spine, soon other joints were involved — knees, shoulders, elbows, wrists and fingers. Trouble then varied from time to time, never very severe, until two months ago, when she had an acute exacerbation in the knees, both becoming red and swollen.

Physical examination showed the right epitrochlear to be the only gland palpable. The tonsils were atrophic. The right shoulder and elbow were tender and motion was limited. Atrophic changes appeared in the finger joints. There was marked swelling of both knees, the right one being the larger and somewhat tender, and presented a distinct fluctuation. Roentgenoscopy of the wrist showed atrophic changes. Cultures from the throat were negative, from the fluid from the knee joint also negative, from the blood, negative. The right epitrochlear gland was removed and three organisms isolated. Autogenous vaccine was started. On discharge after only three injections, she was feeling much better, the anemia was improving and the pain in the knees had decreased and was entirely absent in the other joints.

CASE 11 (4554) —G P. Three years ago, following an attack of grip with tonsillitis, the patient developed acute arthritis in the small joints of the feet; later in the wrists and fingers. These early attacks were associated with chills and acid sweats. Deformity persisted and has gradually progressed. The patient has lost weight and there has been considerable atrophy and progressive weakness of the muscles of the upper extremities. There is at present involvement of the fingers, elbows, wrists and knees, the most active process being in the knees. The tonsils are small but diseased, no other focus of infection being discoverable. October 16, a small lymph node was removed from the right groin for culture with negative result. Section shows a mild chronic lymphadenitis.

CASE 12 (4555) —J E, two years ago, developed acute arthritis in the right wrist, gradually progressive. Since then the process has extended to the elbows, both wrists, fingers and knees and includes the temporomandibular joints. No focus of infection has been found. Repeated blood cultures have been sterile. The most active joints at present are the knees. October 15, a small lymph node was removed from the left groin for culture. Result was negative.

CASE 13 (6530) —B N, aged 40, white. Present illness began two weeks ago with pain in back spreading to hands and knees, these joints becoming swollen. Then in order, hips, ankles, shoulders and elbows were involved. At the time trouble went from one joint to another. Now all are involved.

Physical examination shows irregularity of pupils, pyorrhea, cervical adenitis. The heart is negative. Both shoulders are limited in motion and painful. The right elbow is swollen and tender. The left wrist is tender, motion is limited. All finger joints are similarly affected. There is considerable atrophy of the muscles of the upper extremity. The right knee-joint is the most active. There is some effusion and motion is limited and associated with pain. The left knee-joint is also affected. Von

Age and Sex	Duration	Clinical Diagnosis	Pathologic Diagnosis	Vaccine Therapy and Result	Forms of Bacteria Found	Acid and Antiformin Fast	Agar	Blood Agar	Blood Serum	Bordet
22 ♀	3 mos	Hodgkin's disease	Lymph gran uloma of endothe loid type, fibrosis, ne croses and eosinophils	Improved ?	Diphtheroids	0 Anti formin fast	Dull gray, flat band of discrete delicate colonies	As agar becoming opaque	As agar but glistening and confluent	As agar becoming confluent, spreading and brown
22 ♀	3 mos	Hodgkin's disease	Lymph gran uloma of endothe loid type, fibrosis, ne croses and eosinophils	Improved ?	Diphtheroids	0 Anti formin fast	Glistening, raised, yellow white, smooth, entire band	As agar pinkish, hemolysis slight	As agar	Slightly waxy, flat, dirty gray green band becoming brownish, medium brown yellow, then greenish brown
22 ♀	3 mos	Hodgkin's disease	Lymph gran uloma of endothe loid type, fibrosis, ne croses and eosinophils	Improved ?	Diphtheroids	0 Anti formin fast	Luxuriant, opaque, glistening, white, entire band	As agar more luxuriant, hemolysis + medium becomes brown opaque	As agar more luxuriant	Dirty gray, raised, dull band with glistening edges, becoming brown, medium first, yellow brown then green
30 ♀	1 yr	Hodgkin's disease	Lymph gran uloma of endothe loid and mononuclear type, fibrosis and eosinophils	Yes, Improved ?	Diphtheroids Three slightly varying colonies with same morphology and biology	Antiformin fast (?) 1 hour + 18 hours 0	Delicate, dull, moist, translucent, dirty white band	As agar hemolysis 0	As agar more luxuriant	Thin, moist, gray band
9 ♂	7 mos	Hodgkin's disease	Lymphadenoma of chronic hyperplastic variety	Improvement with Roentgen ray, later bacterins added greater improvement	Seven closely similar diphtheroids M albus	0 Rods not destroyed but not acid fast	Moist, flat, yellow, entire, discrete	Slimy, dirty white, opaque	Faint orange yellow, discrete, sunken colonies, liquefaction +	Slimy, moist, opaque, luxuriant, yellow becoming greenish
9 ♂	7 mos	Hodgkin's disease	Lymphadenoma of chronic hyperplastic variety	Improvement with Roentgen ray, later bacterins added greater improvement	Seven closely similar diphtheroids M albus	0 Rods not destroyed but not acid fast	Delicate, flat, colorless streak	Delicate, flat, discrete colonies	Flat, even, delicate streak becoming yellow	Glistening, moist, pale gray, spreading, becoming brown, medium chocolate late
9 ♂	7 mos	Hodgkin's disease	Lymphadenoma of chronic hyperplastic variety	Improvement with Roentgen ray, later bacterins added greater improvement	Seven closely similar diphtheroids M albus	0 Rods not destroyed but not acid fast	Faint, moist, glistening band becoming yellow, then gray	As agar, but becoming brownish gray	Faint, dry, white band	Luxuriant, dull orange yellow, becoming gray, flat and dry
	7 mos	Hodgkin's disease	Lymphadenoma of chronic hyperplastic variety	Improvement with Roentgen ray, later bacterins added greater improvement	Seven closely similar diphtheroids M albus	0 Rods not destroyed but not acid fast	Faint, dull, yellow white band	Dull, yellow white butyrous	Faint, dull yellow, and dry brown	Thin, dull, flat brown yellow, becoming frosted gray
	7 mos	Hodgkin's disease	Lymphadenoma of chronic hyperplastic variety	Improvement with Roentgen ray, later bacterins added greater improvement	Seven closely similar diphtheroids M albus	0 Rods not destroyed but not acid fast	Glistening moist, raised, yellow, becoming brownish	As agar	Slimy, yellow, depressed, liquefaction = +	Smooth, flat, limited, waxy, pale brown
9 ♂	7 mos	Hodgkin's disease	Lymphadenoma of chronic hyperplastic variety	Improvement with Roentgen ray, later bacterins added greater improvement	Seven closely similar diphtheroids M albus	0 Rods not destroyed but not acid fast	Flat, moist, slimy, pale yellow	As agar but becoming brownish	Flat, smooth, glistening, lemon yellow	Like agar but more luxuriant, distinct brown, chocolate late
9 ♂	7 mos	Hodgkin's disease	Lymphadenoma of chronic hyperplastic variety	Improvement with Roentgen ray, later bacterins added greater improvement	Seven closely similar diphtheroids M albus	0 Rods not destroyed but not acid fast	Faint, dirty white, slimy, translucent band	Faint, smooth, brownish yellow	Limited orange yellow smear	Faint flat, orange band becoming brown waxy

Specimen	Potato	Litmus MBB	Gelatin	Inulin	Acidity Reduction								Hemolysis	Indole	Pigment	Medium Discoloration	Pathogen
					Glu- cose	Lac- tose	Sac- charose	Mal- tose	Man- nitol	Gly- cerol	Dex- trin	Ga- lactose					
Standard	No visible growth	Faintly acid	No visible growth	Alkaline	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	0	0	0	
Standard and control	Spreading filamentous, later slightly raised	Faintly alkaline	Faintly turbid liq 0	Alkaline	++	0 0	0 0	0 0	0 0	0 0	0 0	0 0	+	0	See blood serum	Bordet, greenish brown	
Idiot-like, silent	Dirty white smear becoming raised and yellowish	Faintly alkaline	Faintly turbid liq 0	Alkaline	++	0 0	- 0	0 0	0 0	- +	0 0	0 0	+	0	0	Bordet, greenish, blood agar, brown	
Standard	No visible growth	No change	No visible growth	0	+ 0	0 0	+ 0	0 0	0 0	0 0	0 0	0 0	0	0	0	0	
Idiot-like	Luxuriant, spreading orange	Faintly acid	Luxuriant growth liquefaction +	0	+ 0	0 0	+ 0	+ 0	+ 0	+ 0	0 0	0 0	+	+	Agar, yellow, Bordet, greenish, potato, orange	0	
Standard	No visible growth	Faintly alkaline after 12 days	Faintly turbid at top, liquefaction 0	0	- 0	- 0	- 0	- 0	- -	- -	- 0	- +	0	+	Blood serum, yellow	Bordet, chocolate brown	
Standard	No visible growth	Faintly alkaline	Liquefaction 0	0	+ 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	+	Faint yellow	0	
Standard	No visible growth	No change	Liquefaction 0	0	- 0	0 0	0 0	0 0	0 0	0 0	+ 0	0 +	0	0	Faint yellow	0	
Standard	No visible growth	Acid congo	Liquefaction -	0	+ -	0 0	- 0	0 0	- 0	0 0	+ 0	+ -	+	+	Yellowish	0	Sept. 20, 1918
Standard	No visible growth	No change	Liquefaction -	0	- 0	0 0	0 0	0 0	- 0	- +	- 0	- 0	Slight	-	Yellow brown	Bordet, chocolate brown	
Standard	No visible growth	No change	Liquefaction -	0	- 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	0	Yellow brown	0	

Age and Sex	Duration	Clinical Diagnosis	Pathologic Diagnosis	Vaccine Therapy and Result	Forms of Bacteria Found	Acid and Antiformin Fast	Agar	Blood Agar	Blood Serum	Bordet
22 ♂	4 wks	General adenopathy, probably Hodgkin's disease	Lymphadenoma of chronic hyperplastic variety, no eosinophils or necroses	No	Cocci do not grow into bacillary forms		Scanty, slimy, dirty white	As agar	No perceptible growth	As agar
32 ♀	4 mos	Hodgkin's disease	Endothelioma rapidly growing in lymph channels	Improvement with Roentgen ray, later death	Malbus diphtheroid	0 Rods not destroyed but not acid-fast	Tiny, delicate, colorless, discrete, round colonies	As agar, but growth and medium becoming brown	Flat, dull, yellowish streak	Dull, brown green streak of tiny, discrete colonies, medium beneath, chocolate brown
22 ♀	6 mos	Multiple infectious arthritis with adenopathy		Improvement	Diphtheroids	0 Rods not destroyed but not acid fast	Faint, dirty-white, slimy band	As agar	As agar but whiter	Luxuriant, opaque, other wise like agar
22 ♀	6 mos	Multiple infectious arthritis with adenopathy		Improvement	Diphtheroids	0 Rods not destroyed but not acid fast	Moist, slimy, opaque, raised, orange to salmon to brown	As agar	As agar, but salmon yellow becoming pink coral	Just as agar
41 ♀	7 yrs	General arthritis, anemia with adenopathy		Improvement	Diphtheroid	0 0	Delicate, raised, moist, opaque, glistening, becoming salmon pink	As agar, except color pinkish brown	As agar, except color pale pink	As agar, but color rose pink
41 ♀	7 yrs	General arthritis, anemia with adenopathy		Improvement	Diphtheroid coccus	0 0	Raised, moist, white, tiny, discrete colonies	At first as agar, then hazy gray, then colonies becoming brown	As agar	Dry, brown, discrete colonies tending to coalesce, medium chocolate brown
41 ♀	7 yrs	General arthritis, anemia with adenopathy		Improvement	Diphtheroid coccus	0 0	Yellowish-white, small, discrete colonies	Coalescing, grayish growth becoming brown and scanty	Pearl white, discrete colonies	Dark, dry, greenish yellow band, causing brown green discoloration of medium
54 ♂	4 yrs	Hodgkin's disease	Hodgkin's disease	Marked improvement	Diphtheroids	0 Rods not destroyed but not acid fast	Discrete to confluent, moist, dirty, orange yellow becoming canary yellow	As agar, color changes from yellow to dirty brown, with methemoglobin color of medium	Flat, dry, dirty, orange yellow	Smooth, flat, slightly wavy, spreading, green brown band medium brown
					Diphtheroids	0 Rods not destroyed but not acid fast	Raised, moist, glistening, slimy, canary yellow band	As agar, but orange yellow to greenish becoming brown	As agar	Dry, flat, smooth, opaque, spreading, yellow brown, medium chocolate
48 ♀	1½ yrs	Mediastinal tumor		No improvement	Diphtheroids	0 Rods not destroyed but not acid fast	Raised, moist, slimy, glistening, opaque band becoming brown yellow	As agar, medium dark and opaque	As agar but growth going salmon to orange yellow to coral pink	As agar, growth salmon and then red brown
					Diphtheroids	0 Rods not destroyed but not acid fast	Smooth, moist, glistening gray white band	As agar, hemolysis at top becoming pale and slimy	As agar, but band becoming pale yellow, medium dark under growth	As agar, but growth dirty brownish gray
					Diphtheroids	0 Rods not destroyed but not acid fast	Moist, glistening, dirty white band	As agar, hemolysis	As agar but porcelain white	As agar but velvety lowish becoming dirty yellow brown

No.	Colon	Potato	Litmus Milk	Gelatin	Inulin	Acidity Reduction								Hemolysis	Indol	Pigment	Medium Discoloration
						Glu- cose	Lac- tose	Sac- charose	Mal- tose	Man- nitol	Glyc- erin	Dex- trin	Ga- lactose				
1	+	No perceptible growth	Slightly alkaline, no other change	Liquefaction 0	0	+ 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	+	0	0
2	+	Visible growth	No visible growth	Very faintly acid	Faintly acid	+ 0	0 0	+ 0	- 0	0 0	0 0	+ 0	0 0	0	0	Dull greenish brown	Chocolate brown, green directly under colonies
3	+	Visible growth	No visible growth	Faint acidity	Liquefaction 0	0	+ 0	0 0	+ 0	- 0	+ 0	+ 0	+ 0	0	0	0	Bordet, gray brown
4	+	Visible growth	Salmon yellow	Alkaline reduced	Mucoid sediment liquefaction 0	0	0 +	- 0	0 0	- 0	- 0	- 0	- +	0	+	Yellow, salmon pink	0
5	+	Visible growth	As near	Alkaline, no other change	Liquefaction 0	0	0 +	- 0	- 0	- 0	0 0	- 0	0 +	0	0	Pink	0
6	+	Visible growth	No visible growth	Acid coagulated, reduced	Liquefaction 0	0	+ 0	+ 0	+ 0	- 0	0 0	0 0	+ 0	0	0	0	Bordet, chocolate brown
7	+	Visible growth	No visible growth	Acid coagulated reduced	Flocculent sediment liquefaction 0	0	+ 0	+ 0	+ 0	0 0	0 0	- 0	+ 0	0	0	Agar, yellow, Bordet, yellow brown	Bordet, brown green
8	+	Visible growth	No visible growth	Alkaline, no other change	Heavy flocculent sediment liquefaction 0	-	+ 0	- 0	+ 0	+ -	- 0	- 0	- +	Meth. heino globin	+	Agar, orange yellow, Bordet, green brown	Bordet, brown
9	+	Visible growth	No visible growth	Alkaline	Turbid, heavy, mucoid sediment	-	+ 0	- 0	+ 0	+ 0	- 0	- 0	- +	0	0	Agar, yellow, Bordet, yellow green brown	Bordet, faint chocolate brown
10	+	Visible growth	No change	Faintly acid	-	0	- 0	0 0	0 0	- 0	- 0	- 0	- +	0	0	Yellow, orange, pink brown	Blood agar dark brown
11	+	Visible growth	No change	Faintly acid	-	0	- 0	- 0	- 0	- 0	- 0	- 0	- +	-	-	Blood agar yellow	Blood agar brown
12	+	Visible growth	No change	Faintly acid	-	0	- 0	- 0	- 0	- 0	- 0	- 0	- +	-	-	0	0

Age and Sex	Duration	Clinical Diagnosis	Pathologic Diagnosis	Vaccine Therapy and Result	Forms of Bacteria Found	Acid and Antiformin Fast	Agar	Blood Agar	Blood Serum	Bordet
?	?	Hodgkin's disease	Hodgkin's disease	Marked improvement	Diphtheroids	0 0	Smooth, flat, moist, glistening spreading, pale blue gray	As agar, but at first pink, then brown, then green, hemolysis +	As agar, later liquefying	Flat, limited, discrete colonies tending to coalesce, gray brown to red brown
					Diphtheroids	0 0	Slimy, moist, raised, opaque, faint orange band	As agar, but brownish	As agar, but salmon color becoming coral pink ochre	Moist, glistening, deep orange yellow, becoming ochre
					Diphtheroids	0 Rods not dissolved	Moist, raised, smooth, glistening limited, white	Yellowish white, smooth, flat, glistening, discrete to coalescing	Early as minute, yellow, depressed, discrete colonies, liquefactive +	Raised, moist, glistening, discrete to confluent, raised luxuriant, dirty gray brown
29 ♂	1½ yrs	Hodgkin's disease	Hodgkin's disease	Marked improvements	Diphtheroids	0 Rods not dissolved	Raised, moist, glistening, slimy, dirty white	As agar, pale, hemolysis +	As agar, rather gray, then pink, with greenish fluorescence in medium	As agar, rather gray, then pink, with greenish fluorescence in medium
					Diphtheroids	0 0	Irregular, discrete to confluent, granular, dirty yellow white	As agar, hemolysis slight	Smooth, flat, moist, becoming yellowish	Flat, granular, discrete to confluent, waxy, opaque, gray, lusterless
					Diphtheroids	0 0	Faint, moist, glistening, opaque band	As agar	As agar, but yellow white	Uniform, flat, confluent, gray, with reflection of reddish brown
24 ♂	6 8 wks	Hodgkin's disease	Hodgkin's disease	No continued improvement, patient died	Diphtheroids	0 0	Moist, raised, glistening, opaque, slimy, salmon yellow band	As agar, medium brown	As agar	As agar, medium opaque brown
49 ♂	Auto'y 3 mos duration	Hodgkin's disease	Hodgkin's disease		Diphtheroids	0 Rods not dissolved	Faint, almost invisible band seemingly made up of discrete colonies	As agar, medium opaque	As agar	As agar, growth faint grayish yellow somewhat more luxuriant
					Diphtheroids	0 0	Delicate, dull, moist, dirty white, translucent	As agar	As agar	As agar, becoming more luxuriant, flat, dry, grayish green
					Diphtheroids	0 Rods not dissolved	Faint streak of discrete, yellow colonies	As agar	As agar	As agar, becoming confluent, dirty gray brown, medium chocolate brown
						0	Glistening, pale gray discrete colonies, becoming confluent and whiter	Similar but luxuriant and raised, medium hemolyzed and then darkened	Glistening, confluent, moist, raised band becoming slightly yellowish	Dull, waxy, brownish band, medium becoming brown and without contrast with growth
						0	Luxuriant, glistening, smooth, raised, opaque, dirty white	As agar, more luxuriant and greenish sheen, hemolysis slight	As agar, more luxuriant, raised	Pale salmon pink, raised, glistening, medium becoming dark brown
						0	Glistening, smooth, flat, opaque, greenish white	Glistening, raised, slimy, greenish, hemolysis slight	As agar, more luxuriant becoming lemon yellow	Somewhat flat, slightly waxy, brownish yellow, medium darker

Description	Potato	Litmus	Gelatin	Intrilin	Acidity Reduction								Hemolysis	Indol	Pigment	Medium Discoloration
					Glucose	Lactose	Saccharose	Maltose	Mannite	Glycerin	Dextrin	Gallactose				
No visible growth	No visible growth	All alkaline reduced	Faintly turbid, liquefaction 0	0	+	+	+	+	+	+	+	+	+	0	Greenish, brownish, reddish tinge	0
Not turbid	No visible growth	Alkaline	Turbid, liquefaction 0	0	0	0	0	0	0	0	0	0	0	0	Orange yellow to pink	0
Turbid, no sediment	No visible growth	Congulation faintly alkaline (+), reduction digestion	Liquefaction 0	Acid reduced	+	0	+	0	0	+	+	+	0	0	Yellowish brown	0
Turbid, no sediment	Slimy, dirty white	Alkaline	Turbid, liquefaction 0	0	0	0	0	0	0	0	0	0	+	+	Bordet, fluorescent	See Bordet
Flocculi and granules at bottom	No visible growth	No change	0	0	0	0	+	0	0	0	0	+	0	0	Faint yellow	0
Flocculent sediment	No visible growth	Faint acidity	Mucoid sediment, liquefaction 0	Alkaline	+	+	0	0	0	0	0	0	0	+	Faint yellow	0
Turbid, no sediment	Faint salmon color	Alkaline	Mucoid sediment, liquefaction 0	0	0	0	0	0	0	+	0	+	0	0	Salmon	Browning of blood and Bordet
Faintly turbid, granules at bottom	No visible growth	Faintly alkaline	Faintly turbid, liquefaction 0	0	0	0	0	0	0	0	0	0	0	0	0	0
Very turbid	No visible growth	Faintly alkaline	Faintly turbid, floating flocculi, liquefaction 0	Alkaline	0	0	0	0	0	0	0	+	0	+	0	0
Turbid	No visible growth	Faintly alkaline	Turbid at top, liquefaction 0	Alkaline	0	0	0	0	0	0	0	+	0	+	0	Bordet, chocolate brown
Turbid	No visible growth	No change	Faintly turbid, liquefaction 0	Acid then neutral	0	0	0	0	+	0	0	0	+	0	0	Bordet, brown
Turbid	No visible growth	No change	Faintly turbid, liquefaction 0	Alkaline	0	0	0	0	0	0	0	0	0	0	0	Bordet, chocolate brown

Pirquet is negative. A roentgenogram shows no bone changes in knee and right hand. The Wassermann is negative, the Neisserian fixation-test is negative. The epitrochlear gland is sterile.

Section shows lymphadenoid tissue in a state of chronic follicular and interstitial formation. In the chords and sinuses one may see endothelial and large lymphocyte hyperplasia, and there is a prominence of the vascular endothelium. The connective tissue, both in the gland and in the capsule, is increased, hyaline and poor in cells. Diagnosis, chronic lymphadenitis.

The first two cases (6638, 6640) correspond to the picture accepted as that of Hodgkin's disease, and from them were isolated diphtheroid organisms of quite similar morphology but distinctly differing in biology (Figs 1 to 6). They are similar in Loeffler's stain to R B 2 (Figs 39 and 40), R E 1 (Figs 50 and 51), and K II-3 (Fig 54). Vaccine treatment is now being given in both these cases but no report can be given yet as to its action.

The third case is one of Hodgkin's disease from its history and was so diagnosed by Dr Stengel. The histologic section does not show the picture required but it should be remembered that Roentgen-ray treatment had been used for several months before the gland culture was made. This would probably alter the anatomy of the tissue. From this case no less than seven slightly varying bacteria were found (Figs 7 to 23). Among these Nos 1 (Figs 7 to 10), 4 (Figs 15 to 17), and 7 (Figs 18 to 20) most resemble the cultures in the frank cases of Hodgkin's disease as given above. There are certain similarities between these and some of the cultures of Drs Rosenow and Kolmer.

The fourth case was probably one of Hodgkin's disease although certainly far from typical, only cocci were culturable.

In the fifth case, Patient McC, unfortunately, the culture failed to give a growth and he died so soon after the operation that further work was impossible. It would have been interesting to have gotten a growth in his case because in the next case, another endothelioma, there was a prompt growth of a long rod (8772, Figs 25 to 29). This organism bears no resemblance to any other of my own cultures but is quite like R C 3 (Figs 45 to 47), Dr Rosenow marks this case as one of Hodgkin's disease. This bacterium is not at all like those in my cases of frank Hodgkin's.

From the sixth and seventh cases, diagnosed as tuberculosis by the finding of the bacilli, no rods could be cultivated. The histologic sections from the case of A G F were studied by Gram-Weigert, Giemsa and Much stains. Here and there a solidly staining gram-positive rod (probably a tubercle bacillus) was found, but no granules like the Much granules or rows of beads such as he has described in Hodgkin's disease were seen.

The last five cases are instances of arthritis, from two of which interesting cultures were obtained. 9144-1 (Fig 30) resembles rather closely R B 2 (Fig 40) and R E 1 (Figs 50 and 51), and is like a small example of 8916-9 (Figs 21 and 22), while 9392-1 (Figs 32 and 35), although drawn with difficulty because of its poor staining properties, is similar to 6640 (Fig 5). Neither of these cases even remotely resemble Hodgkin's disease and it is noteworthy that diphtheroids were found in them.

GENERAL DISCUSSION

Examination of the charted characters, the morphology notes and the pictures reveals a bewildering variety of organisms, closely related diphtheroids and a few cocci. To dispense with the latter it may be pointed out that they were *M. albus* in two cases (8772 and 8916), two slightly varying streptococci in an arthritis case (9392) and a large diplococcus in a possible Hodgkin's case (9265). In this instance the remark of Dr. Rosenow may be recalled, to the effect that cocci predominate in the more recently enlarged glands. This glandular enlargement was only of four weeks' duration.

Consideration of the diphtheroids fails to show any two alike, and as has been suggested in discussing the case groups there is no marked similarity between cultures isolated from closely related pathologic conditions, with the possible exception of the two frank Hodgkin's cases, 6638 and 6640. In the first of these two there were three pseudodiphtheria bacilli, one of which resembles morphologically the single bacterium isolated from 6640, being distinct in its cultural characteristics.

It does not seem profitable to attempt any conclusions from this series of 13 cases even in conjunction with the material given me by Dr. Rosenow and Dr. Kolmer, further than to state that no one bacterial variety with definite morphologic and cultural characters has been isolated from eleven cases diagnosed as Hodgkin's disease (Rosenow 5, Kolmer 2, my own cases 4) to which may be added a case of endothelioma of the lymph nodes. Diphtheroid bacilli have been isolated from glands in at least two cases having no clinical or anatomic resemblance to Hodgkin's disease and from Case C of Dr. Rosenow, an instance of mediastinal tumor. Much work will be necessary to establish the microbial cause of Hodgkin's disease especially in the direction of immunology. This I have already begun but I have not as yet sufficient data to make it worth discussing. Two of the cases have failed to show agglutination of the bacteria isolated in them and one did not bind complement with the patient's serum.

A study of the duration of enlargement of the gland supplying the cultures and the bacteriologic result reveals nothing. The position of the gland seems to have nothing to do with the kind of organism

isolated In the Hodgkin's and similar cases material was removed from the inguinal region twice, axilla and mastoid region each once The endothelioma was in the cervical glands The arthritis cases giving positive cultures supplied respectively an axillary and epitrochlear gland The position of these last two glands is such that drainage from the throat and genital tract, the common habitats of diphtheroids, is probably excluded as a means of their recent reception However, they probably entered through one of these places at some time

The glands of the patients in the two frank Hodgkin's cases and the tuberculous adenitis case, A G F, have been studied by the Much, Gram-Weigert and Ziehl-Nielson stains Tubercle bacilli have been found only in the last case No Much granules, either single or in rows were found in the first two By the Much method a few diphtheroids were found in 6640 as pale rods with poorly staining, large, blue granules No metachromatic bodies were found Only one rod was found in the Gram-Weigert preparations and it was nearly solidly blue

The material presented here may be summed up as follows

Diphtheroid rods may be isolated from Hodgkin's disease and other adenopathies, but there is no uniformity in biology and morphology among the strains isolated by three observers from clinical and pathologic Hodgkin's disease Diphtheroid rods, similar in biology and morphology to those found in Hodgkin's disease, may be found in enlarged glands in cases of chronic atrophic arthritis and other conditions

Diphtheroids have been found in glands the seat of a neoplasm (8772), and in the enlarged glands near a neoplasm (R C) There is great similarity in all respects between the gland diphtheroids and those found in normal and pathologic seats in the body, the so-called pseudodiphtheria bacilli More facts are demanded to show the exact relation of the diphtheroids to Hodgkin's disease

In one case, in which autogenous vaccination was given a fair trial, the patient has died

Another patient, already improving under the Roentgen ray, continued to improve with autogenous vaccination and no Roentgen ray In arthritis cases the patients receiving vaccine consisting wholly or in part of diphtheroids, showed some improvement

Much granules have not been found in sections of lymph granulomas of the Hodgkin's type

The cases used in this work were in the services of Dr Stengel, Dr Frazier, and Dr A C Wood at the University Hospital I wish to thank these gentlemen for the use of the material

I am indebted to Mrs V C Brogdon for much assistance in running through cultures and for the preparation of the chart, and to Miss L H Irwin for the drawings

THE DIMINISHED POWER OF THE NEPHRITIC KIDNEY FOR ELIMINATING URIC ACID AS EXEMPLIFIED BY THE USE OF ATOPHAN¹

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It is presumed that in normal and gouty individuals atophan induces an augmented output of uric acid in the urine and a decreased concentration in the blood (and tissues) by endowing the renal cells with an increased power for eliminating uric acid.¹ In nephritis,² accordingly, the renal cells, which have become abnormal and whose work has been impeded by interstitial growth, would be expected to respond less readily to this stimulus. In the present communication are presented six cases of nephritis, which illustrate the diminished, or entire absence of any, effect of atophan on the concentration of uric acid in the blood.³

The observations in Case 1 were made before the onset of marked uremic symptoms. The reduction in the uric acid concentration of the blood following the use of atophan is relatively slight, in accordance with which there is no demonstrable increase in the urinary uric acid. Other blood findings and the very low phenolsulphonephthalein output give further evidence of inefficient renal functioning.

Case 2, taken at a more advanced stage than Case 1, while uremic symptoms were pronounced, disclosed no reaction to atophan whatever. This is significant in view of the failure of any injected phenol-sulphonephthalein to reappear in the urine, and the notable retention of urea and creatinin as well as uric acid in the blood.

Case 3, clinically, was in far better condition during the period of observation than the two cases above discussed, although a week later the patient suddenly developed convulsions and died. One notes that on two occasions there were moderate responses to the administration of atophan. The urinary findings are not always in good agreement with the blood changes, but this is attributed to faulty collection and

¹ Submitted for publication April 28, 1915.

² From the Laboratory of Pathological Chemistry and the Department of Medicine of the New York Post-Graduate Medical School and Hospital.

³ *J. Biol. Chem.*, 1914, 19, 219.

² *Chem. and Pharmacol. Exper. Therap.*, 1913, 1, 539.

³ We are indebted to Dr. R. A. C. and W. G. Louch for many courtesies and to Mr. Adolph Berthold for the technical assistance.

TABLE 1—SLIGHT EFFECT OF ATOPHAN IN NEPHRITIS (CASE 1, T D)
BEFORE ONSET OF MARKED UREMIC SYMPTOMS *

Day	Uric Acid in Urine gm	Uric Acid in Blood mg per 100 c c	Atophan gm per day
1	0.13	68	1
2	0.16		
3	0.13		
4	0.21		
5	0.08		
6	0.11		
7	0.14		
8	0.09	60	3
9	0.13		3
10	0.13		3
11	0.11		
12	0.07		
13	0.10		
14	0.07		
15	0.16		

* Male, aged 34 years. Diagnosis, advanced interstitial nephritis with marked cardiac hypertrophy. Blood pressure, 230 (systolic), 130 (diastolic), phenol-sulphonephthalein output, 3 to 4 per cent (two determinations), urine 0.2-0.3 per cent albumin, moderate number hyaline and granular casts. Other blood findings: urea N, 100, creatinin, 8 mg per 100 c c. Died six weeks after conclusion of the observations. Diagnosis confirmed at necropsy and by histological examination.

TABLE 2—ADVANCED CASE OF NEPHRITIS (CASE 2, K K) WITH NO REACTION TO ATOPHAN *

Day	Uric Acid in Blood mg per 100 c c	Atophan gm per day
1	12.3	1†
2		2
3	12.5	2

* Female, aged 39 years. Diagnosis, chronic interstitial nephritis (uremia). Blood pressure eight days before death, 265 (systolic), 140 (diastolic), phenol-sulphonephthalein output, 0 (two determinations), urine large amount of albumin. Other blood findings: urea N 148, creatinin, 15 mg per 100 c c. No edema. Died day after conclusion of above observations.

† After taking blood

TABLE 3—MODERATE RESPONSE TO ATOPHAN IN CASE OF NEPHRITIS
(CASE 3, J W) CLINICALLY IN GOOD CONDITION *

Day	Uric Acid in Urine Daily Averages gm	Uric Acid in Blood mg per 100 c c	Atophan gm per day
1	0 15	81	
2-5			
7			2
8			2
9			4
10	0 24	60	4
11			4
12-16			
17-29	0 15		
30	0 17	70	1 †
31			1 5
32	0 15		3
33			3
34			3
35			4
36			
36-40	0 24	5 4	
44		7 2	

* Male, aged 34 years. Diagnosis, chronic interstitial nephritis. Blood pressure, 170 (systolic), 100 (diastolic), phenolsulphonephthalein output, 4 per cent in two hours, urine, approximately 0.1 per cent albumin, occasional hyaline and granular casts, few pus cells. Other blood findings: urea N, 50, creatinin, 6 mg per 100 c c.

† After taking blood

TABLE 4—NO RESPONSE TO ATOPHAN IN NEPHRITIS
(CASE 4, S H) *

Day	Uric Acid in Blood mg per 100 c c	Atophan gm per day
1	77	
2		
3		3
4		3
5	80	4

* Male, aged 37 years, interstitial nephritis (uremia). Phenolsulphonephthalein output, 1 per cent in two hours, urine: moderate amount albumin, occasional hyaline and granular cast. Other blood findings: urea N, 70, creatinin, 10 mg per 100 c c. Slight edema of extremities. Patient died six weeks after observations were concluded.

TABLE 5—DEFINITE RESPONSE TO ATOPHAN IN NEPHRITIS (CASE 5, J P) CLINICALLY IN GOOD CONDITION *

Day	Uric Acid in Blood mg per 100 c c	Atophan gm per day
1	67	
2		
3		2
4	60	3
5		3
6		2
7	43	
8		
9	57	
12	68	

* Male, aged 34 years, chronic diffuse nephritis Phenol-sulphonephthalein output for two hours, 43 per cent Urine moderate amount albumin, many hyaline and granular casts Other blood findings urea nitrogen, 25, creatinin, 25 mg per 100 c c Wassermann + + + +

TABLE 6—DECIDED RESPONSE TO ATOPHAN (CASE 6, L S M) *

Day	Uric Acid in Blood mg per 100 c c	Atophan gm per day
1	50	2‡
2†		3
3		3
4	27	
7	40	

* Female, aged 23 years Subacute parenchymatous nephritis Blood pressure, 110 (systolic), 65 (diastolic), phenolsulphonephthalein output, 31 per cent in two hours, urine moderate amount albumin, occasional hyaline and granular cast, few pus cells Other blood findings urea nitrogen 22, creatinin 25 mg per 100 c c Pregnant four months previous to present study, at which time edema was present No edema during above period of observation

† On this day the milk contained 27 mg uric acid per 100 c c ‡ After taking blood

inadequate preservation of the urine. The urea and creatinin concentrations of the blood indicate a less pronounced retention than that observed in the two previous cases.

Case 4 showed no response whatever to the administration of atophan, which is in harmony with the pronounced retention of creatinin and the negligible output of phenolsulphonephthalein. The clinical prognosis is an early fatal termination.

Case 5 shows a definite response to atophan, to the extent of a reduction of blood uric acid of 2.4 mg per hundred c.c. This favorable sign falls in with the moderate retention of urea nitrogen and creatinin and the quite good output of phenolsulphonephthalein. Clinically, the case at present appears not to be in a serious condition.

In Case 6 the response to atophan is quite decided, which is of interest in connection with the fair elimination of phenolsulphonephthalein and the but slightly increased urea and creatinin concentrations of the blood.

It is evident that in these six cases there is a general relationship between the degree of response to the administration of atophan on the one hand, and the extent of non-protein nitrogenous retention and the clinical pictures on the other. While we hesitate, on the basis of these all too few cases, to formulate definite conclusions, the observations do appear to us to lend some support to the view enunciated in the opening paragraph of this paper that abnormal renal cells would be expected to prove less responsive to the action of atophan than are healthy cells.

After a part of our data had been accumulated, the paper of Frank and Pietrulla⁴ came to our attention. They reported four abnormal kidney cases, in which atophan was employed. In their first case (contracted kidney) the uric acid concentration of the blood was reduced from 3.0 mg per hundred c.c. to 0. In their second case (bilateral cystic kidney) it was reduced from 1.5 to 0. The low concentrations of blood uric acid in these two instances indicate that they were not the type of case in which the kidneys would be expected to offer opposition to the action of atophan. In their third case (contracted and cystic kidney) the uric acid concentration of the blood was not determined before atophan was given, but since after the administration of the drug the moderately high value of 4.78 mg per hundred c.c. was noted, they considered the previous existence of a higher concentration as improbable. This is an unjustified stand, as indicated in our present studies and by several others elsewhere reported,⁵ in which

⁴ Frank and Pietrulla. *Arch. f. Exper. path. u. Pharmacol.*, 1914, LXXVII, 361.

⁵ Myers and Fine. *Jour. Biol. Chem.* 1915, XX, 391.

values of 8 to 15 mg per hundred c c of blood were commonly observed In their fourth case (subacute nephrosis) they describe the atophan effect by reporting many typical crystals before and fewer after the use of the drug The results of Frank and Pietrulla, above reviewed, appear too indecisive to throw light on the question of the dependence of an atophan response on the condition of the renal cells

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CHRONIC MENINGOCOCCUS SEPTICEMIA ASSOCIATED WITH PULMONARY TUBERCULOSIS [†]

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The earlier clinical and pathologic studies of certain infectious diseases, among others, pneumonia, typhoid fever, gonorrhea and epidemic meningitis, indicated a marked predilection of the specific excitant to localize in certain definite tissues. The introduction of more accurate methods for clinical investigation, and of additional refinements in bacteriologic technic have afforded substantial evidence that the distribution of the causal agent in such disorders is not so limited as was formerly presumed.

Following the identification in 1887 of the *Meningococcus intracellularis* by Weichselbaum¹ as a separate species, and the establishment of its specific relation to epidemic meningitis, investigations were conducted to determine the presence of this microorganism in the blood and in the lesions complicating this disease.

The biologic characteristics of the meningococcus rendered such investigations particularly difficult. The susceptibility of the organism to outside influences and its intracellular position made it difficult to cultivate under the most favorable conditions. Bacteria other than the meningococcus frequently encountered in such investigations often obscured the cultural characteristics of the meningococcus by the production of a more luxuriant growth, and thus led to negative findings. It has also been quite definitely determined that certain bacterial species, among others, the *Micrococcus catenalis* of Pfeiffer, the gonococcus, certain strains of the *Diplococcus flavus*, *Micrococcus pharyngius siccus*, *Diplococcus crassus*, *Micrococcus cinereus* and pseudomeningococcus are similar to the meningococcus in their morphology, tinctorial reactions and occasionally in their intracellular position.

Investigators at present are agreed that the microscopic findings alone are inadequate for purposes of differentiation, and that data regarding the cultural characteristics and biologic activities of the organism are necessary before a bacteriologic diagnosis can be made with any degree of certainty. The many alleged reports of the pres-

* Submitted for publication May 5, 1915.

[†] Read before the Saranac Lake Medical Society, at Saranac Lake, N Y, Dec 9, 1914.

¹ Weichselbaum Fortschr d Med, 1887.

ence of the meningococcus in parts removed from the central nervous system, or in the circulating blood, must therefore be accepted with reserve if the identification rests merely on microscopic examination

Antedating the discovery by Weichselbaum of the specific nature of cerebrospinal fever, Gaucher² in 1881, in an epidemic of meningitis, observed numerous cocci in the cerebral exudate, blood and urine Ughetti³ in 1883 demonstrated cocci in the spinal exudate and blood in a case of meningitis The brief bacteriologic notes included in both the above reports do not permit a definite opinion regarding the nature of the organism described In 1905 Martini and Rohde⁴ reported two cases of meningococcus septicemia occurring in epidemic meningitis They state that to their knowledge this is the first instance in which the organism has with certainty been microscopically and culturally demonstrated in the blood Cochez and Lemaire,⁵ 1901, are credited by Kutscher⁶ as the first to report an authentic case of meningococcus septicemia In an epidemic of cerebrospinal fever they examined the blood eleven times and obtained positive findings in two cases Duval,⁷ Boviard⁸ and others, however, concede the claim of priority to Gwyn⁹ who reported in 1899 a case of epidemic meningitis complicated by arthritis A gram-negative diplococcus was recovered from the synovial and spinal exudates, and from the blood The organism isolated by Gwyn displayed the ability to grow on solid gelatin, a characteristic which Albrecht and Ghon,¹⁰ Weichselbaum,¹¹ Kutscher,¹² Kolle and Wassermann¹³ and others have failed to demonstrate as belonging to the meningococcus With this one exception, the evidence appears conclusive that the organism isolated in this case was a true meningococcus

Meningococcus septicemia accompanying or secondary to meningitis has been reported by Lenhartz,¹⁴ Marcovitch,¹⁵ Robinson¹⁶ and

2 Gaucher, quoted by Weichselbaum Kolle and Wassermann's Handb d path Mikroorg, Edit 1, iii

3 Ughetti, *ibid*

4 Martini and Rohde Berl klin Wchnschr, 1905, xlii, 997

5 Cochez and Lemaire Baumgarten's Jahresbericht, 1902, xviii, 91

6 Kutscher In Kolle and Wassermann's Hand d Path Mikroorg, Edit 2, iv

7 Duval Jour Med Research, 1908, xix, 258

8 Bovaird THE ARCHIVES INT MED, 1909, ii, 267

9 Gwyn Bull Johns Hopkins Hosp, 1899, x, 112

10 Albrecht and Ghon Wien klin Wchnschr, 1901, xiv, 984

11 Weichselbaum Handb d path Mikroorg, Edit 1, iii

12 Kutscher Munchen med Wchnschr, 1906, No 20

13 Kolle and Wassermann Klin Jahrb, 1906, xv

14 Lenhartz Deutsch Arch f klin Med, 1905, lxxxi, 81

15 Marcovitch Wien klin Wchnschr, 1906, xiv, 1312

16 Robinson Am Jour Med Sc, 1906, cxxxi, 603

others Elser¹⁷ in a careful study of forty-one cases of cerebrospinal fever recovered the intracellular diplococcus from the blood in ten, or approximately 25 per cent

Duval⁷ states that a careful review of the literature of meningococcus septicemia would seem to indicate that septicemia due to the meningococcus is invariably secondary to meningitis. It has, however, been definitely established that meningococcus septicemia can occur with no evidence of a previous or existing meningitis.

The following case reported by Andrews¹⁸ in 1906 is of special interest in this respect

A physician, aged 50, suddenly developed a few spots on the face and within a few hours was covered from head to foot with a profuse hemorrhagic purpura. The temperature was 99.4 F, respirations 34 per minute, pulse not perceptible at the wrist. The appearance of the patient suggested a profound sepsis. He lapsed into unconsciousness and death occurred twenty-four hours from the onset of the illness. There were no meningeal symptoms. The result of the blood examination made shortly before death showed large cocci on the blood films, which were exclusively intracellular, and the blood culture yielded a gram-negative coccus which corresponded in every detail to the diplococcus of Weichselbaum. At necropsy there was no macroscopic or microscopic evidence of meningitis. The case, however, was of very short duration, and of a fulminating type.

Cecil and Soper¹⁹ have more recently described an interesting case of meningococcus endocarditis with septicemia. The complete bacteriologic data included in this report leave no room for doubt as to the identity of the organism. At postmortem the meninges and brain appeared normal. Microscopic sections of the various parts of the cortex, pons and medulla showed a normal pia arachnoid and offered nothing suggestive of an exudate.

A number of further cases have been selected from the literature as they present clinical pictures similar in many respects to the case to be described. In 1902 Salomon²⁰ reported the following case

The patient, a woman, aged 32, complained of pain and swelling in the hands, elbows and knees. These symptoms were followed by chills and fever. A few days later, owing to the septic appearance of the patient and the presence of a skin eruption, a blood culture was taken and submitted to Professor Marx of the Royal Institute for Experimental Therapy at Frankfurt, who reported the organism to be a meningococcus. The condition of sepsis continued over a period of eight weeks, with no evidence of meningitis or focal involvement except a slight splenic enlargement. Successive fresh crops of a multiform eruption appeared resembling erythema nodosum, petechia and at times a syphilitic or typhoid roseola. The nodules on the feet were tender to pressure. Eight weeks after onset, typical symptoms of meningitis developed. The collected fluid removed by lumbar puncture contained gram-negative diplococci, mostly intra-

17 Elser Jour Med Research, 1905, vii, 89

18 Andrews Lancet, London 1906 lxxxv 1172

19 Cecil and Soper THE ARCHIVES INT MED 1911, viii 1

20 Salomon Berl Klin Wchnschr, 1902, xxxv, 1045

cellular The culture from the spinal fluid proved sterile The patient eventually recovered after an illness of more than four months

The description of the organism isolated is as follows It grew only at incubator temperature on nutrient agar and blood agar By continued cultivation of the organism a growth was eventually obtained on plain agar Transplants to plain bouillon, gelatin and potato were negative The coccus was gram-negative, biscuit shaped and was occasionally observed in short chains Mice remained healthy after a subcutaneous injection of one platinum loopful of a suspension of agar culture in bouillon, but death resulted after an intraperitoneal injection of the same amount

No serum reactions were recorded As there is no record of a lumbar puncture having been made previous to the development of the meningeal symptoms, the presence of meningitis early in the disease cannot be excluded with certainty One is forced, however, to believe that the meningococcus septicemia antedated the meningitis or that the meningeal involvement remained latent over a period of two months before manifesting symptoms

Liebermeister²¹ reported the following case in 1908

A laborer, aged 59, was admitted to the hospital Feb 25, 1908, complaining of general malaise with pain and stiffness in both shoulders The patient claimed to have had inflammation of the lungs on two previous occasions The statements of the patient were conflicting and the mentality was not entirely clear Definite signs of pulmonary involvement were present, and the spleen was slightly enlarged The symptoms and fever were of the septic type Repeated crops of small papules and rose-like spots appeared The knee and elbow joints were painful, stiff and contracted There was no evidence of meningitis After an illness of four months the patient finally recovered Several cultures from the blood yielded the meningococcus The spinal fluid remained normal Repeated examinations of the sputum failed to show tubercle bacilli, but contained numerous pneumococci The organism isolated conformed in all essentials to Weichselbaum's coccus The administration of Wassermann's serum previous to the agglutination tests invalidates to some extent the positive results obtained

As the patient recovered, meningitis cannot be excluded, but the sterile spinal fluid and absence of meningeal symptoms constitute strong evidence that no meningeal involvement occurred

Fukuhara²² summarizes a report by Handa and Nanjo of an epidemic of cerebrospinal fever occurring in a regiment stationed at Osaka

The nine cases comprising the epidemic were studied clinically and bacteriologically in detail Five of the cases were to be looked on as suffering from a bacteremia, in four, the meningococcus was cultivated from the blood One of the cases showed first on the twenty-first day, a second on the twenty-third day, and a third after several months, the typical symptoms of cerebrospinal meningitis The cerebrospinal fluid, which was at first quite clear, and bacteria-free, became turbid and contained the diplococcus of Weichselbaum

21 Liebermeister *Munchen med Wchnschr*, 1908, 1v, 1978

22 Fukuhara *Centralbl f Bakteriologie und Parasitenkunde*, 1914, No 3, p 82

The authors conclude from their observations that epidemic meningitis begins as a bacteremia, and that the meningeal symptoms follow as a later manifestation

SUMMARY OF AUTHOR'S CASE

Patient A D, aged 39, Canadian, married, linotypist, had an irrelevant family history. His wife and four children are well. One infant died of convulsions eight years ago. He uses tobacco and alcohol moderately. Venery is denied.

Past History—Except for the early diseases of childhood and occasional attacks of acute indigestion, the patient enjoyed excellent health until May, 1913, when he had general malaise—cough with considerable expectoration and loss of weight, and complained of pain at the base of the right lung. The sputum was blood-streaked on several occasions and contained tubercle bacilli. The patient entered Iola Sanatorium where he remained two months and was then referred to us for further treatment. He presented on examination a slight involvement at the right apex and dense infiltration at the corresponding base, otherwise the examination was negative. Excellent progress was made during a treatment period of seven and one-half months, and the patient was discharged April 16, 1914, with the pulmonary condition arrested. He remained well for three months, when he had a chill with temperature following a prolonged exposure to a cold, drenching rain on a fishing expedition. Patient returned to work on the second day, but as the chills and fever recurred, applied to the sanatorium for readmission, July 5, 1914. The patient appeared obviously toxic and complained of severe pain in the legs. Temperature 103.2 F, pulse 102, respiration 24. The next day and for two subsequent days, he was quite comfortable, when the symptoms and pain again appeared. Urgent family matters arose at this time, which made it imperative for him to return home for a period of six weeks. Dr. Trembley has kindly supplied me with the following notes of the case during this interval. The patient was free from symptoms and worked for two weeks after leaving the sanatorium, when he again ventured on a second fishing expedition, was exposed to an all day cold rain, which resulted in a return of the chills and fever. From this date, similar attacks recurred, at first, two to five days apart, but toward the end of August, daily. The symptoms suggested malarial fever, but repeated examinations of the blood failed to show the plasmodium. Leukocytes, 13,000, polymorphonuclears, relatively and quantitatively increased. The administration of large doses of quinin and aspirin seemed to influence the symptoms and temperature favorably.

On September 8 the patient again came under our observation. Only the more important findings are here recorded. He was greatly emaciated, having lost at least 30 pounds since last seen, he was somewhat prostrated and appeared acutely ill. The features were blanched but not cyanotic. He responded intelligently to questions. The pupils were equal and reacted to light and accommodation. There were no ocular palsies. Ears, nose and throat were normal. The pulmonary condition failed to present any evidence of recent activity. The size and position of the heart was difficult to define, owing to the pulmonary lesion, but apparently no hypertrophy of the organ existed. At the cardiac apex a faint systolic murmur transmitted toward the axilla for a short distance was heard. Other valvular orifices were intact. The pulse was 96, regular of fair volume, the arterial wall was soft. No enlargement of the spleen was made out on palpation or percussion, and the abdomen contained nothing worthy of note. The superficial and deep reflexes were slightly accentuated. The knees, elbows and some of the smaller joints of the hands were flexed stiff, slightly swollen and painful, with no reddening of the overlying skin. The anterior surface of both tibiae and the muscles of the extremities

were decidedly painful to light pressure, the large nerve trunks were not. There was a diffuse multiform eruption of the skin, more abundant on the arms and legs, irregularly distributed, and composed for the most part of macules or slightly raised papules, which showed a pigmented center and hyperemic zone, the spots varying in size from a pinhead to 3 cm in diameter. In the older spots the hyperemic zone had been replaced by a discolored area or was entirely lost, giving to the latter a flea-bite appearance. On both thighs anteriorly and on the right leg there were a few large hyperemic nodules, which were exquisitely tender and resembled erythema nodosum. On the abdomen and back, a few rose spots typical of a typhoid roseola were seen. The face and the mucous membranes of the mouth and nose were free from the eruption. The bowels were regular, the appetite poor, temperature 103 F, respiration 20, pulse 96.

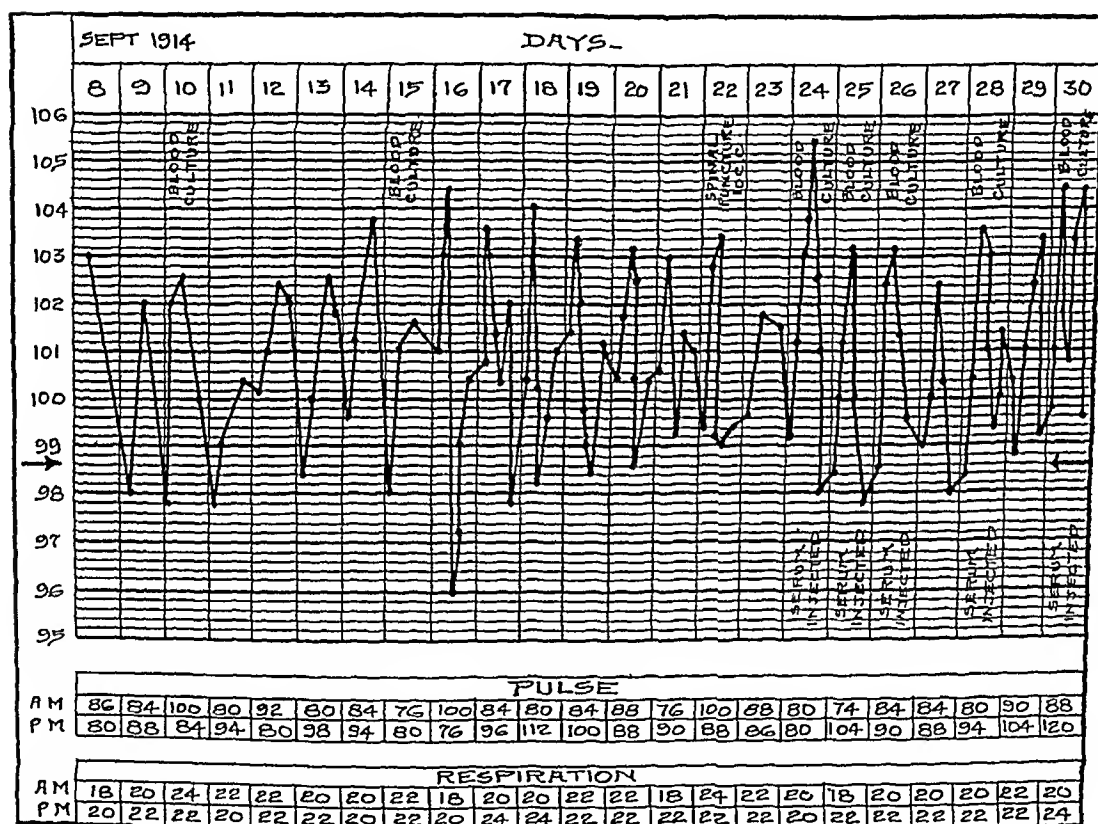


Chart 1—Patient's pulse, temperature and respiration record during September, 1914

September 9 Cough and expectoration are slight. The sputum, mucopurulent, 10 cc in twenty-four hours, contained tubercle bacilli. There was no thoracic pain or obvious dyspnea. Leukocytes, 13,900, polymorphonuclears, 75 per cent, red blood cells, 4,100,000, hemoglobin, 80 per cent.

September 10 The quiescent condition of the tuberculous lesion and the absence of local symptoms pointing to an acute respiratory disorder, would incline one to believe that the patient's condition could not be satisfactorily explained on the basis of a recrudescence of the pulmonary lesion. This idea was further enforced by the unusual clinical course which presented features foreign to a tuberculous infection. The septic appearance of the patient, associated with a cardiac murmur, petechial eruption and involvement of several joints suggested a wide generalization of the causal agent, the blood presumably

acting as the channel of distribution. A blood culture²³ was taken. Ten c c of blood were withdrawn from the median vein, and immediately transferred to a flask containing 150 c c of plain bouillon.

September 12. Swelling and tenderness of the left testicle appeared. An ice cap was applied. Patient was somewhat weaker and complained bitterly of pain in both tibias. Morphine was required to alleviate the pain.

September 15. Swelling and pain in the testicle has completely subsided. The accompanying temperature chart illustrates the intermittent type of fever. Increase of symptoms accompanied the rise in temperature, but the mentality of the patient, though clouded, was not more than would accompany the degree of fever present. The knees and elbows remained slightly flexed and could not be fully extended without producing considerable pain. No exudate into the joints had occurred and the overlying skin was not inflamed. The blood culture of September 10 was positive. Microscopically and culturally the coccus isolated conformed in all essentials to the diplococcus of Weichselbaum. A detailed report of the bacteriologic findings is found elsewhere in this article. Second blood culture, 10 c c, was made to verify the bacteriologic report. Leukocytes 13,100.

September 16. The patient's condition is not noticeably changed. Fresh crops of eruption appear, more abundant on the thighs. The unexpected nature of the organism disclosed and its invariable association with meningitis made us repeat the examination of the nervous system in detail. The eyes showed no abnormal change. Examination of the cranial and spinal nerves elicited nothing of note. There were no areas of anesthesia, hyperesthesia or paresthesia. The deep and superficial reflexes remained somewhat accentuated. Babinski and Brudzinski signs were negative. Owing to the flexed condition of the knees and pain on extension, no opinion could be formed as to the presence or absence of Kernig's sign.

September 18. There was a systolic murmur over the pulmonic area, the mitral murmur was very faint. The ratio between the pulse and temperature was definitely altered, the pulse rate rarely exceeding 110 with a temperature registering 104 F or above. A few small hyperemic papules on the fingers of the right hand and a solitary large red nodule, 3 cm in diameter, on the inner side of the same elbow were noted. The skin over the metacarpophalangeal joint of the little finger was reddened and the joint was swollen and tender. No definite chills had as yet been noticed.

September 22. Ten c c of spinal fluid were withdrawn. The fluid was not under pressure and was of an opalescent appearance. A scarcely visible precipitate was formed after centrifuging for ten minutes. Stained smears of the sediment showed a few leukocytes, red blood cells, but no bacteria. The sediment was planted on ascitic broth and blood agar. No growth appeared. The cell count and chemical tests were not carried out. A sterile swab was inserted through the mouth into the nasopharynx. The culture obtained yielded gram-positive and gram-negative cocci, the cultural behavior of the latter conformed to the *Micrococcus catarrhalis*. Fresh crops of the eruption with the characteristics already described appeared from time to time. Leukocytes 18,500. The urine showed a slight trace of albumin. Diazo and indican reactions were negative.

23. Technic. The anterior surface of the elbow joint was scrubbed with green soap and sterile water, followed by a 1:1,000 solution of mercuric chloride, alcohol and ether, then thoroughly dried with a sterile swab, and tincture of iodine applied. The arm above the elbow was sufficiently compressed by a Bier's bandage to produce an engorgement of the median basilic or cephalic vein, which was selected for taking the culture. A sterile all glass Luer syringe (15 c c capacity) and No 18 or 19 needle were used. Sterile rubber gloves and gown were worn by the operator.

September 23 Certain features of the case, more especially the septic course of the disease, complicated by a polyarthritis, orchitis, cardiac lesion and the presence of gram-negative cocci in the blood suggested a systemic gonococcus infection. The culture taken from the urethra after a thorough massage of the prostate yielded a gram-positive coccus. Complement fixation test for the gonococcal infection was negative. A second culture from the nasopharynx yielded a staphylococcus. Unsuccessful attempts were made to demonstrate intracellular cocci on blood smears. An antiseptic solution for the nose and throat was ordered. The second blood culture of September 15 yielded the meningococcus.

September 24 The well-recognized value of serum treatment in epidemic meningitis suggested its employment in the present instance. One c.c. of anti-meningococcus serum²⁴ was injected subcutaneously to determine if any hypersensitiveness existed on the part of the patient for this particular serum. As

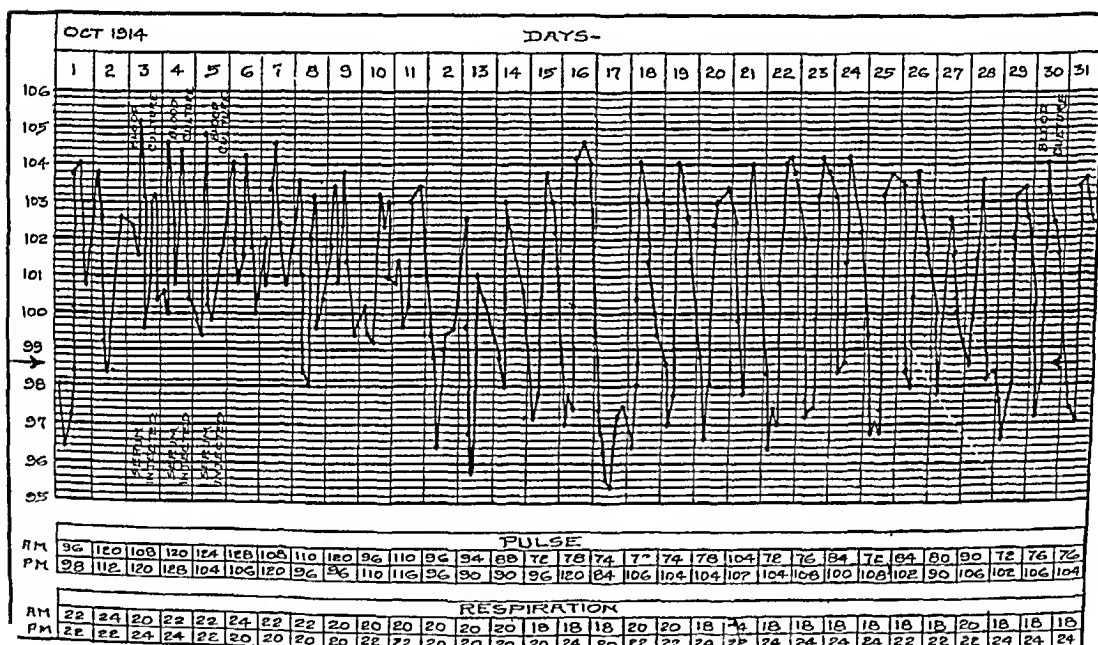


Chart 2—Patient's pulse, temperature and respiration record during October, 1914

no local or general reaction followed after four hours, 20 c.c. of the serum were administered intravenously. Before the injection of the serum and in all future administrations, 10 c.c. of the blood were first removed for bacteriologic study. The serum was given entirely by the intravenous method. The patient was alarmed and nervous during the administration of the serum. The temperature rose in a few hours to 105.2 F, the highest since admission.

September 25 The patient asserted that he was decidedly better, and the temperature was lower than for the past few days. A detailed examination of a specimen of deep sputum forwarded to the laboratory on the 24th failed to show the meningococcus and contained no tubercle bacilli. The index finger of the right hand was painful, red and swollen. Antimeningococcus serum, 20 c.c., was administered.

September 26 Serum, 25 c.c., was given. The patient was very nervous during the administration, complained of retrosternal pain following the injec-

²⁴ New York City Board of Health antimeningococcus serum

tion, and had a slight chill for about twenty minutes Patient appeared weaker and appetite was much impaired

September 28 Serum, 35 cc, was given Forty-five minutes after the administration a chill of ten minutes duration occurred and was followed by profuse sweating

September 30 Forty cc of serum were given, a chill occurred, followed by profuse sweating

October 1 The patient was very drowsy and weak, and complained of distressing pain in the legs Morphine was administered There was a slight systolic murmur at the apex Indistinct murmurs were also heard over the pulmonic and aortic regions The pulse was regular, of fair volume Swelling of some of the metacarpophalangeal and phalangeal joints of both hands was noted An urticarial rash over the left elbow and right knee was seen

October 3 Serum, 40 cc, was administered Shortly after the administration of the serum a chill of twenty minutes occurred

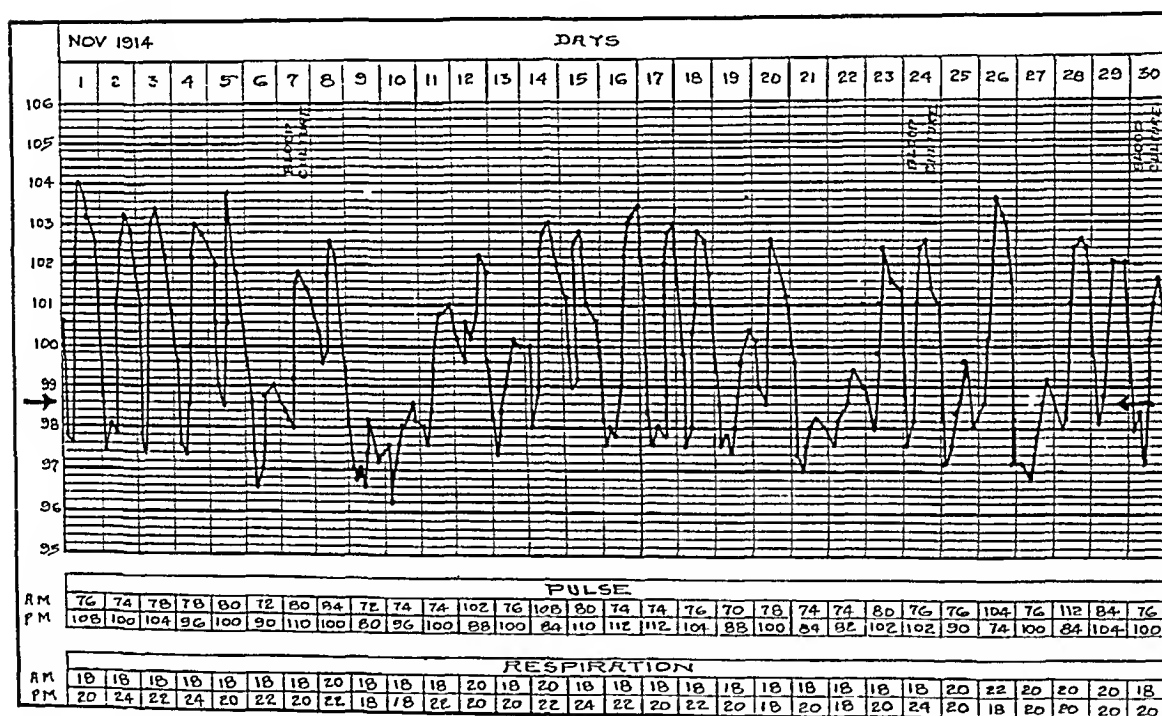


Chart 3—Patient's pulse, temperature and respiration record during November, 1914

October 4 Serum, 40 cc, was given The injection was followed almost immediately by a rigor, half and hour in duration The pulse rate increased from 100 to 130 The patient was much prostrated His arm was slightly swollen and a circumscribed urticarial rash appeared over the site of the previous injection The swelling and stiffness had lessened in the elbows and smaller joints of the hands

October 5 Serum, 40 cc, was given Following the introduction of the serum a marked rigor with collapse occurred and for a few hours the patient was in a precarious condition As the last blood culture was reported positive, it appeared advisable, on account of the alarming symptoms that apparently followed the employment of the serum, to discontinue its use

October 10 Patient felt somewhat better but still complained of exquisite pain in both tibias A few of the papules on the hands became pustular, but stained smears of their contents and inoculations on Loeffler's serum proved negative

October 15 The eruption completely disappeared The heart was free from murmurs

October 17 Patient was very ill, subnormal morning temperature Blood pressure systolic, 92, diastolic, 65

October 22 Patient was much better A few fresh papules appeared on the skin Faint murmur was heard over the mitral and pulmonic areas No definite rigor occurred since serum was discontinued No activity in the lung lesion can be detected

October 30 Fresh papules were usually ushered in with an abrupt rise in temperature No fresh petechial spots appeared during the past week A blood culture was taken Tuberculin O T 00001, intracutaneously

November 2 The tuberculin reaction was positive The blood culture of October 30 was also positive

November 7 A blood culture was taken Severe headache existed for a few hours The cardiac murmurs were indistinct, the eruption disappearing

November 15 Eruption had completely disappeared, the appetite was good, the patient much better There were no cardiac murmurs The blood culture of November 7 was positive

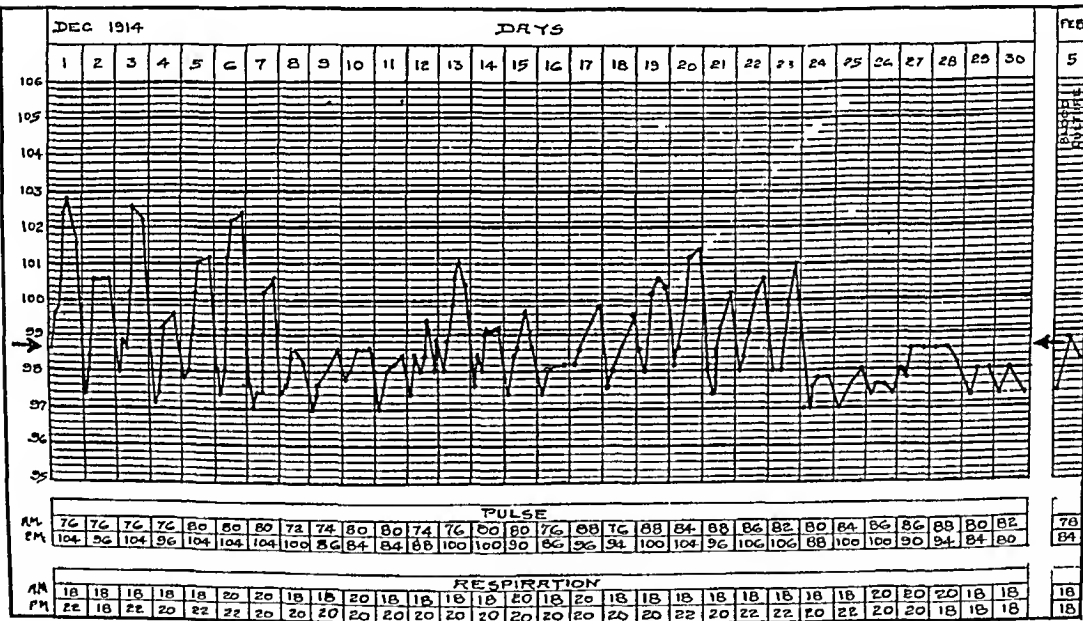


Chart 4—Patient's pulse, temperature and respiration record during December, 1914

November 24 No tubercle bacilli were found in the sputum The improvement was noticeable A faint systolic murmur was heard at the apex and over the pulmonic area A blood culture was taken Blood pressure, systolic 108, diastolic 62

December 7 Except for slight stiffness in the fingers, there is no evidence of the previous joint involvement The patient appeared much improved, had gained in weight and the appetite was excellent, but the blood culture of November 30 was reported positive Convalescence was uninterrupted and rapid The patient was discharged Jan 10, 1915 The general condition was good, there were no symptoms, the mitral murmur was indistinct

Feb 5, 1915 After a two weeks' convalescent period at home, the patient resumed his former occupation and at present is doing full work He states that he is feeling very well, has no symptoms and is not unduly fatigued at the end of a day's work The temperature has remained normal since the date of dis-

charge His general condition is excellent, his weight 140 pounds The pulmonary lesion is quiescent, the signs fewer than at any time since the patient has been under observation, and one would be almost inclined to believe, from the results of the examination, that the meningococcus septicemia had had a salutary effect on the pulmonary lesion The cardiac valves are apparently intact No murmurs have been detected The cardiac action is regular, rate 74 The blood culture of February 5 proved negative

To summarize briefly The illness extended over a period of more than five months, with a known septicemia of three months' duration The fifteen blood cultures yielded the meningococcus The spinal fluid was sterile The disease was characterized by a septic course, multifocal eruption and cardiac murmurs which later disappeared The course of the infection was apparently not influenced by the administration of the serum

BACTERIOLOGY

Morphology and Staining—The organism stains well with the ordinary anilin dyes and is decolorized by the Gram method of staining In appearance it is biscuit shaped, arranged in diplo or tetrad forms and occasionally in small agglomerations No chain formation was noted Marked variation in the size and staining qualities of the organism are observed on the same slide By Neisser's method of staining, Babes-Ernst bodies cannot be demonstrated

Cultural Characteristics—Ascitic agar twenty-four-hour growth shows colonies circular, slightly convex, with smooth, fairly distinct outlines The average diameter of the colonies is 2 mm, but considerable variation of size is observed The colonies enlarge by continued cultivation Viewed by reflected light the colonies are gray or grayish white in color and present a smooth, moderately glistening surface By transmitted light some appear as fairly uniform gray disks, others have a grayish white or faintly yellow center, surrounded by a more or less translucent zone The growth is somewhat viscid, but is not adherent to the medium

Microscopic Appearance—Examined with a low power lens, the colonies appear uniformly circular, with an entire or undulating border The center of the colony is brownish yellow and granular, the periphery is structureless and translucent On the second or third day, crystalline deposits occur in the granular structure of the colony, which has now become coarser in appearance

On blood-agar (sheep) the growth is luxuriant Guinea-pig blood-agar—first transplant—shows a luxuriant growth Ascitic bouillon shows slight cloudiness with a gradually increasing deposit and pellicle formation Fragments separate from the pellicle and fall to the bottom Dextrose agar—first transplant shows scant or no growth On plain bouillon the younger generations grow more sparsely than on ascitic bouillon Dextrose calcium carbonate broth gives a luxuriant growth which retains its viability for many weeks at 37 C, with the

formation of a brownish-yellow pigment after the fourth week. On milk growth takes place without producing coagulation. Gelatin shows no growth at room temperature.

Attempts to grow the organism on the above mentioned mediums at room temperature were unsuccessful.

*Carbohydrate Fermentation Reactions*²⁵—Dextrose, +, Maltose, +, Levulose, —, Galactose, —, Lactose, —, Saccharose, —

Opsonin Reaction—Patient's Serum Meningococcus (stock) 1 200 +, 1 500 ±, Meningococcus (patient) 1 200 +, 1 500 —, Parameningococcus 1 20 ±, 1 50 —

Agglutination—Patient's Strain Board of Health (New York City) anti-meningococcus serum, at 56 C for twenty-four hours 1 10 ++, 1 20 ++, 1 50 ++, 1 100 +, 1 200 —

Half of a twenty-four hour agar culture injected intraperitoneally kills young guinea-pigs (115 gm) in twenty-four hours, showing, at necropsy, typical peritonitis similar to that described by Flexner for the meningococcus.

The morphology, growth on ordinary mediums, rapid autolysis in fresh cultures are characteristic of the meningococcus. The pathogenicity and biologic reactions check with the meningococcus.

When the characteristic symptoms of a disease caused by a known specific excitant are wanting, it is quite justifiable to question the identity of the organism isolated unless definite proof is forthcoming that it conforms in all particulars to the specific organism. In the present instance, the bacteriologic data appear sufficient to warrant designating the micro-organism recovered as a true meningococcus.

If one be correct in presuming that the nature of the organism in this case has been satisfactorily established, it is difficult to explain the source of infection, since no reported cases of cerebrospinal fever existed in the neighborhood in which the patient lived for months previous to the onset of the illness. The possibility that direct infection, that is, from person to person, occurred, must, however, be considered, even in the absence of cases of epidemic meningitis, since Kutscher¹² was able to demonstrate the presence of meningococci in the throats of healthy individuals four times, apart from epidemics and when no connection with sporadic cases could be determined. Contact with a meningococcus carrier must therefore be considered a possible source of infection, and the determination in the present case of a meningococcus carrier would have been of decided value in establishing the probable source of infection, but owing to the delay in diagnosis, and also to the fact that the meningococcus is only a temporary resident of the nasopharynx it is very probable that an investigation to determine this point would have resulted in failure.

²⁵ Hiss serum water, + = acid

The many investigations of the past few years to determine the portal of entry of the meningococcus proved unsuccessful, until the discovery of Albrecht and Ghon¹⁰ that the nasal secretions of patients suffering from epidemic meningitis harbored the meningococcus. This observation was soon confirmed by a number of observers, including Flugge,²⁶ Kolle and Wassermann²⁷ and von Lingelsheim²⁸

In the majority of cases of epidemic meningitis the presence of sore throat and the absence of any other focus of infection corroborated the view that the organism gains access to the meninges through the nasopharynx from this point. Westenhoffer²⁹ makes the statement that every case of epidemic meningitis is first a case of meningococcus pharyngitis. In twenty-nine cases of epidemic meningitis coming to necropsy, he was able to demonstrate an acute pharyngitis in every instance. Meyer³⁰ in a detailed study of thirty-two cases of this disease found a well-marked inflammation of the nasopharynx in twenty-four. Kophch³¹ quotes Goodwin and Sholly to the effect that the organisms can be recovered from the nasal mucus in 50 per cent of the cases during the first two weeks of the disease, and in 10 per cent. of those who come in contact with patients. It therefore appears fairly well established that the upper respiratory tract is the usual portal of entry for the meningococcus. No evidence of a nasopharyngeal inflammation could be determined in the present case, but this fact would not be sufficient in itself to exclude the nasopharynx as the portal of entry.

The presence of a long-standing lesion of the lung in the present case might reasonably be considered as affording excellent conditions for the entrance of the meningococcus into the body. This view is strengthened by the fact that at necropsy the meningococcus has been reported associated with a pulmonary lesion. The failure in the present instance to demonstrate the intracellular coccus in the sputum or the pharyngeal secretion makes it difficult to state with any degree of certainty the probable channel selected by the meningococcus in gaining access to the blood stream.

Although opinions regarding the portal of entry in epidemic meningitis may be said to be unanimous, the question as to the paths selected by the meningococcus in reaching the brain still remains under discussion. The theory of direct extension, that is, from the nasopharynx by means of the lymphatics, to the meninges of the brain, finds many

26 Flugge *Klin Jahrb*, 1906, xv, No 2

27 Kolle and Wassermann *Klin Jahrb*, 1906, xv, No 2

28 Von Lingelsheim *Klin Jahrb*, 1906, xv, No 2

29 Westenhoffer *Berl klin Wchnschr*, 1905, xlii, 737

30 Meyer *Klin Jahrb*, 1906, xv

31 Kophch *In Osler's Mod Med*, ii, 499

active exponents, notably Westenhoffer,³² Meyer³⁰ and von Lingelsheim²⁸ Elser and Huntoon³³ in an exhaustive study of epidemic meningitis, are inclined to favor the blood stream as the avenue selected by the meningococcus in reaching the brain, and summarize the evidence in favor of a hemotogenous origin as follows

(1) The early generalization of the bacteria as shown by the anatomic findings in individuals who succumb within twenty-four hours, (2) the early appearance of the meningococcus in the blood in some instances, and (3) the simultaneous occurrence of symptoms referable to the brain, and to structures more or less removed from the central nervous system

To further support this view, they attempted to show that the mode of onset of the disease is incompatible with the assumption that it gains access to the brain by direct extension. They also advance experimental evidence in favor of a hemotogenous mode of infection. The present case would appear to furnish further evidence in favor of the view advanced by Elser and Huntoon³³

In view of the relatively few reported cases of primary meningococcus septicemia, it is difficult to determine the value of any of the therapeutic measures employed. The efficacy of antimeningococcus serum in epidemic meningitis suggested that this form of therapy might also prove of value in meningococcus septicemia.

Liebermeister's²¹ patient received one intravenous injection of 20 c c of Wassermann's serum, but no statement follows concerning the action of the serum on the disease.

Cecil and Soper¹⁹ gave 15 c c of Flexner's serum subcutaneously and the following day repeated the dose intravenously. The serious condition of the patient previous to the first injection precludes an opinion of its value in this case. The authors state that the first injection was without effect.

Bovaird⁸ administered Flexner's serum four times during a period of five days in a case of meningococcus septicemia with sterile spinal fluid. Twenty c c were given intradurally, 25 c c intravenously and 60 c c subcutaneously. The blood culture before the first injection of the serum and in all subsequent cultures proved sterile. The author believes that it is not justifiable to assume from the fact that the blood proved sterile, that the organism had altogether disappeared from the blood before the introduction of the serum. From clinical observation he concludes that the serum played an important part in the improvement and ultimate recovery of the patient.

32 Westenhoffer *Berl klin Wchnschr*, 1906, xliii, 1267

33 Elser and Huntoon *Jour Med Research*, 1909, xv, 373

In the present case, 260 c c of antimeningococcus serum were administered intravenously during a period of twelve days. The initial dose of 20 c c was gradually increased until the maximum of 40 c c was reached.

The introduction of the serum was followed in each instance, after a period varying from twenty minutes to a few hours, by an increase in the severity of the symptoms. The presence of an urticarial rash, increase of pain in the joints and rigors with marked prostration conformed in many respects to the symptoms observed in serum sickness.

The severity of symptoms, together with the fact that the blood cultures still remained positive, suggested the advisability of discontinuing this form of treatment.

It must not be inferred, however, from our experience, that antimeningococcus serum might not be an available form of therapy in this type of case. The established chronicity of the disease before the employment of the serum, selection of dose and time interval between the injections might prove to be the deciding factors in explaining the conduct of the serum in our hands.

In the absence of any well-defined focal lesion, and in view of the protracted nature of the illness, the term "chronic meningococcus septicemia" would appear appropriate in designating the condition in the present instance. The case reported by Liebermeister is strikingly similar to the present case in the chronicity of the disease, the presence of a multiform eruption appearing in successive crops, multiple arthritis without the formation of an exudate, and associated with muscular contraction, moderate leukocytosis, and a septic type of fever. Liebermeister suggests that the above symptoms enable one to determine the accessory symptoms of meningitis; that is, those due to the general infection and not to the focal lesion.

I have been unable after a rather careful review of the literature to discover any mention of meningococcus septicemia associated with clinical pulmonary tuberculosis, and it would be hazardous on the basis of a single case to formulate any definite conclusions regarding the behavior of the pulmonary lesion in the presence of this type of septicemia. One would expect that any disorder characterized by a protracted and septic course, associated with an extreme degree of emaciation, would exert a harmful influence on the pulmonary condition. However, a study of the signs and local symptoms indicate that apparently no activity in the pulmonary lesion has occurred. The patient retained the allergic state, reacting moderately to an intracutaneous injection of 0.0001 c c of original tuberculin, which might throw some

light on the question as to why the pulmonary condition in the present instance did not suffer

In conclusion, the presence or absence of an accompanying meningitis in the present case is a question that must fail of absolute solution since postmortem examination is the final word in its establishment

I wish to express my thanks to the medical staff for many helpful suggestions, to Dr S Flexner, Dr M Wollstein and Dr O T Avery for performing the serologic tests and checking the bacteriologic work, to Dr A McNeil of the Department of Health, New York City, for the fixation test for gonococcal infection and to Mr M Morita for invaluable aid in carrying out the bacteriologic and other laboratory tests

TREATMENT OF CYSTINURIA

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Cystinuria is a rare but very interesting disease. Its chief interest is from the point of view of body metabolism and the various careful studies of this disease have added much to our knowledge of protein katabolism. The treatment of the disease has received but little consideration.

Cystinuria has a definite symptom-complex and may be readily diagnosed. The symptoms are those of renal stone, and differ but little from those of other types of renal-stone disease. Certain features, however, are somewhat characteristic.

- 1 The stones are usually very small. They are sharp edged, rough, with a color and texture very similar to that of a small piece of maple sugar.

- 2 The stones tend to occur in the urine in showers, usually after a period of high protein ingestion.

- 3 The amount of blood in the urine is often out of proportion to the symptoms and to the size and number of stones.

The diagnosis of cystinuria is readily made by microscopic examination of the urine. Cystin appears in the form of flat hexagonal crystals. These are insoluble in weak acids, but are readily soluble in weak alkalies.

The treatment has been almost entirely dietary. Alsberg and Folin¹ in a striking piece of work, proved that the amount of cystin excreted in the urine, in a case of cystinuria, varied directly with the amount of protein consumed. They do not believe that there are different degrees of severity of the disease but that the amount of cystin excreted depends on the amount of protein consumed, plus the protein katabolized from the wear and tear on body tissues. For this reason it is not possible to get the urine of a cystinuric free from crystals. On a diet which contained practically no protein, the amount of cystin excreted was very small. At the end of thirteen days, however, the patient was not cystin-free.

The practical application of these facts in the treatment of cystinuria is self-evident. The patients should be kept on a low nitrogenous

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¹ Alsberg and Folin. *Am Jour Physiol*, 1905, xiv, 54.

diet In the subsequent treatment of their patient, Folin was able by these means, to keep him free from symptoms for over a year Most patients, however, chafe under the restrictions of a low protein diet, and are willing even to suffer from renal colic, rather than bear the monotony of the nitrogen-poor regimen Furthermore 30 to 50 gm of protein a day is minimum for normal metabolism, and this amount causes a considerable excretion of cystin

Cystin is so readily soluble in weak alkali, that it seemed plausible to treat cystinuria by the addition of sodium bicarbonate to the diet This empirical treatment only needed a patient for its justification Curiously enough two of these cases were studied at about the same time and treated by the same method, one by Klemperer and Jacoby² in Berlin and one by myself The report of Klemperer's case, however, was published in March, 1914, and since this treatment was similar to mine, though my conclusions are at variance from his, it was thought advisable to defer publishing my studies for a year, meanwhile keeping the patient under observation

Klemperer's patient had a typical history and symptom-complex The studies are briefly reported The patient was first placed on a rich protein diet No estimation of the nitrogen intake or of the urinary nitrogen is recorded The cystin both precipitated and in solution was determined by Gaskell's³ method They found a total of 716 mg of cystin on the fifth day of the high protein diet

The patient was then put on a very low protein diet for three days The average excretion of cystin was 78 mg This they called the "endogenous cystin" Finally a mixed diet was given The nitrogen intake or excretion is not stated From 6 to 10 gm of sodium bicarbonate were added to the diet each day The cystin both in the precipitate and in solution rapidly decreased and on the fifth day none was present in the urine These results are very striking, and their conclusions are that the alkali does not act as a solvent for cystin, but actually influences metabolism of the body so that cystin is not excreted or even formed

The patient studied by us had a characteristic history

Patient 812, a white printer, unmarried, aged 22, was entered as complaining of gravel present in the urine for twenty months

Family History—The patient's father is living and is said to have tabes dorsalis His mother, one brother and three sisters are living and well No tuberculosis, cancer, diabetes or kidney trouble occur in the family He denies venereal disease He uses a moderate amount of tea, coffee and tobacco, but no alcohol

Past History—Patient's health has always been poor He had scarlet fever with a cardiac complication at an early age At 8 years of age he had rheumatic

2 Klemperer and Jacoby *Therap d Gegenw*, 1914, lv, 101

3 Gaskell, J F *Jour Physiol*, London, 1907, xxxvi, 142

fever and chorea and was ill for eight or nine months. Rheumatic fever recurred every spring for two or three years. Two years ago he was operated on at the Boston City Hospital for appendicitis and inguinal hernia and made a satisfactory convalescence.

Present Illness—Six months after the operation the patient passed a small stone in the urine. This was soon followed by many others. Several patent medicines were tried, without relief. In August, 1913, the patient went to the Boston City Hospital with complete anuria, which he said had existed for three days. He was in the hospital three days, during which time he passed no urine. Being of a stubborn and intractable disposition, he refused cystoscopy or operation. He was discharged against advice and walked home. On the journey, "something gave way" and during the day he passed over "a gallon" of urine. The patient was seen by us first in January, 1913, when he came to the Peter Bent Brigham Hospital outdoor department. His chief symptoms then were pain in the lower lumbar region, pain over the symphysis pubis and blood and gravel in the urine.

Physical Examination—The patient's weight was 110 pounds, he was poorly developed, though fairly well nourished. The heart was slightly hypertrophied, with a high-pitched systolic murmur at the apex. The abdomen showed slight tenderness in the costovertebral angle on both sides. No abdominal masses or tenderness were made out. Examination otherwise was negative. The urine showed large numbers of typical cystin crystals and a small amount of blood, but no casts. Blood pressure was normal, hemoglobin, 95 per cent, and white blood cell count, 10,000.

The patient was admitted to the house for metabolic study Jan 31, 1914. The following data was recorded: intake of fluid, intake of nitrogen, output of urine, specific gravity of urine, the reaction of the urine as measured by the hydrogen ionization method, output of total nitrogen, urea, uric acid, ammonia, total sulphates and inorganic sulphates. (The results are shown in the table.)

The hydrogen ionization was determined according to the colorimetric method of Henderson and Palmer⁴. The factor 74 represents the reaction point of blood, the most alkaline figure, 84, is definitely pink to phenolphthalein. The diet was standardized by Locke's⁵ tables. The urinary nitrogen, urea, uric acid and ammonia were determined by the microchemical methods of Folin⁶ and his associates. The total sulphates and inorganic sulphates were determined by the method of Folin.

Alsberg and Folin⁷ have shown that cystin is best quantitated by the determination of neutral sulphur. Ethereal sulphur was not determined since it remains constant. On 119 gm protein intake the normal average excretion of ethereal sulphur as SO_3 is 0.22 gm in twenty-four hours. The normal average of neutral sulphur as SO_3 is 0.17 gm. In cystinuria there is a marked increase in the neutral sulphur, which is due to the sulphur of cystin.

The patient was put on a standard diet containing 10.5 gm of nitrogen. He remained on this diet two days before the records were begun. His blood examination showed

Nonprotein nitrogen	280 mg per 100 cc of blood
Urea nitrogen	140 mg per 100 cc of blood
Uric acid	14 mg per 100 cc of blood
Creatinin	12 mg per 100 cc of blood
Creatin	100 mg per 100 cc of blood

The creatinin and creatin determinations were made by Dr. W. Denis.

On February 5, 2 gm of cystin were given to the patient. This was excreted at once as inorganic sulphur, substantiating the observation of Alsberg and Folin,

4 Henderson and Palmer Jour Biol Chem, 1912, xiii, 363

5 Locke Food Values, New York, D. Appleton & Co., 1911

6 Folin, O Jour Biol Chem, 1912, xi, 493

RESULTS OF URINE EXAMINATION IN PATIENT WITH CYSTINURIA

Date	Intake Fluid, c c	Volume Urine, c c	Hydro gen Ioniz	Total Nitro-gen, Gm		Urea N	Ammonia N	Uric Acid	Total Sulphur as SO ₃	Inor ganic SO ₃	Undeter mined SO ₃	Remarks
				Intake	Output							
2/3/14	3,000	710	7.3	10.5	10.56	8.02	0.334	0.72	1.78	1.14	0.64	Standard diet
2/4/14	1,950	1,020	7.4	10.5	11.52	8.68	0.234	0.50	1.89	1.19	0.69	Standard diet
2/5/14	1,650	810	7.2	10.5	10.87	8.78	0.319	0.31	2.73	1.98	0.75	Plus 2 gm cystin
2/6/14	2,100	970	7.2	10.5	10.24	8.69	0.313	0.45	1.70	1.09	0.61	Standard diet
2/7/14	1,900	1,550	8.2	10.5	10.47	9.39	0.540	0.56	1.98	1.08	0.90	Standard diet and 40 gm sodium bicarbonate
2/8/14	1,750	1,660	8.4	10.5	9.50	8.10	0.506	0.55	1.64	0.907	0.73	Standard diet and 40 gm sodium bicarbonate

that cystin is katabolized, and not absorbed and excreted unchanged. On the 7th, 40 gm of sodium bicarbonate were added to the diet. This was repeated on the 8th. This treatment was followed by a slight increase in the neutral cystin sulphur, rather than a decrease, as noted by Klemperer. The striking thing that occurred, however, was that despite the increase in cystin sulphur, cystin crystals at once disappeared from the urine. This could be due to but one thing, namely, alkalinity of the urine.

Klemperer states that in his case cystin disappeared from the urine both in the precipitate and in solution, in our case the cystin simply went into solution. It seems hardly reasonable to suppose that sodium bicarbonate can influence body metabolism since Henderson⁷ has shown that even very large amounts of alkali added to the blood do not influence its reaction. It has been suggested that in Klemperer's case, the cystin was present in the urine, but was in solution, and the method used did not detect it in the presence of the alkali.

The results from giving 40 gm of sodium bicarbonate were definite and satisfactory, but needless to say, a patient cannot take 40 gm nor even 10 gm of sodium bicarbonate every day without digestive and other disturbances. In a previous unpublished experiment on hydrogen ionization of the urine, we have found that it required from 8 to 12 gm of sodium bicarbonate a day to keep the urine definitely alkaline, that is, below 7.4, when on a diet of from 10 to 12 gm of nitrogen. The higher the total nitrogen, the more alkali required. The practical solution is obvious, a low nitrogen diet which will offer some variety, with small amounts of sodium bicarbonate to keep the urine alkaline.

Our patient declined to tolerate any further quantitative metabolic experiments, but it has been possible to follow him clinically. He was put on a 5 to 6 gm nitrogen diet with 4 gm of sodium bicarbonate a day, given some litmus paper and told to keep the urine at a point where the litmus always turned blue.

Subsequent History—The patient reported at frequent intervals. Whereas he had been having all the symptoms of renal stones, colic, constant pain in the back radiating down to the groin, hematuria, etc., he was now entirely free from these symptoms. An occasional crystal could be found in the urinary sediment. He passed no stones until August when he broke his strict dietary rules eating large amounts of meat and fish. He passed 20 or 30 stones within two or three days, and suffered considerable pain and distress.

Following this period it was thought best to give the patient one protein day a week. The low nitrogen diet was taken every day but Friday. On this day he was given 10 or 12 gm nitrogen together with from 12 to 14 gm of sodium bicarbonate. The patient was better satisfied and free from symptoms.

In February, 1915, one year after the metabolic studies had been made, the patient was given 10 or 12 gm of nitrogen a day for one week, without sodium bicarbonate. At the end of three days there was a return of all symptoms, with the passage of 50 to 75 small stones and showers of typical crystals in the urine.

The patient was then put on the regimen suggested by Klemperer, 10 to 14 gm of nitrogen a day with 10 gm of sodium bicarbonate a day. At the end of two weeks, cystin crystals were readily found in the urine, and an occasional small stone was passed, furthermore the large doses of bicarbonate were not well tolerated by the stomach. He voluntarily returned to the regimen of six low protein days and one moderate protein day. Beginning March 2, 1915, he was given a diet containing 10 to 12 gm of nitrogen and 12 to 15 gm of sodium bicarbonate. After five days the urine was found to be alkaline to litmus, with only an occasional cystin crystal in the sediment. Total cystin determined by a new colorimetric method in Dr. Folin's laboratory showed 0.6 to 0.7 gm of cystin. This experiment furnishes conclusive evidence, that in our case at least, cystin is being excreted in such an amount as would be expected from the nitrogen intake, but is rendered soluble by the alkali.

7 Henderson, L. J. Jour Biol Chem, 1909, vi, 29

CONCLUSIONS

1 Cystinuria is best treated by a low protein diet, with the addition of sufficient alkali to keep the urine alkaline

2 Cystin crystals will practically disappear from the urine of a cystinuric when sufficient sodium bicarbonate is added to the diet to render the urine alkaline

3 The amount of sodium bicarbonate necessary to render the urine alkaline, when the patient is on a nitrogen intake of 10 gm , or more, is greater than can be well borne by the stomach

4 Sodium bicarbonate does not influence body metabolism in cystinuria but simply renders the cystin soluble

I desire to thank Dr Folin for his many helpful suggestions in this study

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SYPHILIS AND RAYNAUD'S DISEASE [†]

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The coincidence of syphilis and Raynaud's disease has occasionally been observed. A few cases have been reported in which the diagnosis of Raynaud's disease was unwarranted, and in which we were dealing with a pure specific obliterative endarteritis, in other cases in which the diagnoses are beyond question, the interdependence is very frail and uncertain, and we might more correctly speak of a simultaneous occurrence, but several instances must be admitted in which the etiologic rôle of an acquired or inherited syphilis is extremely suggestive.

The following case is deemed worthy of record because confusing complications early in the course of the disease obscured the diagnosis, but chiefly because it adds another illustration to this curious group of cases.

History—The history concerns a colored girl 7 years old, whose present illness began Feb 5, 1914.

Family History—The mother has had six miscarriages and a Wassermann test on March 21, 1914, was positive. The father denies lues. A brother and sister of the patient, both younger, seemed normal and showed no luetic stigmata on physical examination.

Past History—The patient's birth was normal. She had suffered from otorrhea at 2 years of age, and had had spells of earache since then. At 5 years of age she had measles, mumps and whooping cough. Otherwise she had been healthy and normally active.

Present Illness—Feb 5, 1914, the mother noticed that the child walked "straddled legged," and examination disclosed a vaginal discharge. Three days later she commenced limping on the right foot and complained of intense pain in her right knee, so that she was confined to her bed, and when seen Feb 11, 1914, her temperature was 104 F. Vaginal smears showed a Neisser infection. The right knee was swollen, tender, and motion was limited, due to pain. No other joints were involved. Feb 18, 1914, the patient was admitted to the medical service of the Washington University Hospital. Temperature, 103 F., leukocytes, 45,000.

Physical Examination—Forty-six inches long, patient crying, restless, facies show pain, looks ill, is emaciated, muscles small, panniculus absent, complains of cold in a comfortably heated ward. Examination negative except for slightly enlarged tonsils, notched lower incisors, enlarged cervical glands, rapid pulse, and the following interesting condition of the extremities. The right knee

[†] From the Medical Clinic of Washington University Medical School, St Louis.

enlarged and very tender, definite fluctuation, patella floating, left knee not swollen, the right foot shows a black swollen area, including all the foot laterally from the base of the great toe across to the outer side of the heel, including the whole dorsum of the foot as high as the malleoli. There is a sharp line of demarcation with a narrow red margin, especially on the sole. The left foot showed a similar area, extending from between the great and second toes to the middle of the lateral border of the foot, including all four outer toes. Discoloration is dark chocolate over the toes, light brown over the other parts. The ankles are not swollen or tender. The pulse is readily felt in the posterior tibials and dorsalis pedis artery of each foot.

February 20 the Widal test was negative. The right knee was aspirated and about 30 cc of a thick purulent fluid removed. Smears showed almost exclusively polymorphonuclear leukocytes. Careful search failed to reveal any organisms and cultures on various media were sterile. Repeated blood cultures were likewise sterile. The fever gradually subsided, the leukocytes falling steadily. Under treatment the vaginal discharge cleared up. The knee was kept in extension from February 24 to March 8 and a roentgenogram of the knee joint taken March 22 showed apparently a normal joint. It seems reasonable to conclude that we were dealing with a gonorrheal vaginitis, complicated by an acute gonorrheal arthritis of the right knee joint.

On admission and for the first four days thereafter, the patient exhibited a peculiar craving for carbohydrate foods, constantly crying for bread, crackers and cake, even asking for them when in pain and even at night. The first three days after admission the patient's urine showed a partial reduction of Fehling's solution, an atypical Nylander's test, was fermented by yeast, and polarized light to the right. Repeated examinations since that time have been consistently negative for sugar, even though on one occasion 100 gm of white bread were given at a single meal. Thus we were dealing with a transient glycosuria probably alimentary.

Two days after admission the Wassermann test gave complete fixation of complement and the patient's serum was again strongly positive April 11 and June 23. With the positive Wassermann of the mother and a history of six miscarriages we are justified in a diagnosis of congenital lues.

We now come to the chief feature of interest, the discoloration of the feet, which eventually developed into a perfectly symmetrical gangrene. Just before admission there had been a spell of very cold weather with considerable snow on the ground. Thinking the condition might be frost bite, careful inquiries were made from the family as to the possibility of exposure to cold. They insisted that the house had been warm and felt reasonably certain that the child had not been in the snow.

Further inquiries elicited the important fact that on Jan 15, 1914, the patient's left hand became cold and swollen suddenly, the fingers showing a sharply demarcated black discoloration. After two or three days this disappeared only to reappear two days later. This same phenomenon occurred in the hospital, the first time February 24, lasting ten days, with pain, swelling, redness, tenderness and itching of all the fingers going on almost to blackness of the index finger of the left hand. The radial vessels were pulsating, the same condition recurred April 7, clearing up over night.

The process on both feet gradually progressed, the skin becoming ashen gray, finally black, dry, shriveled, the gangrene extending proximally and the line of demarcation assuming a permanent position March 28, almost six weeks after the onset of symptoms. The great toe of the left foot amputated itself April 2, the remainder up to the proximal phalanges dropped off April 15. The process was slower on the right foot, but a symmetrical portion was involved and was removed by a little manipulation June 29. The final result illustrated the wisdom in a case of dry gangrene of permitting a natural demarcation in preference to an amputation. Had a surgical attempt been made it would have

been necessary to sacrifice a great deal more of the feet than the patient was able to save for herself

Antiluetic treatment was instituted soon after admission and consisted in mercurial inunctions for almost three months. June 29, 0.2 gm old salvarsan was administered intravenously, 0.25 gm on July 8, 0.3 gm, July 14, and 0.3 gm, July 29. This therapy had no effect in curing or checking the disease of the feet, and such a result could not be reasonably expected, even if the congenital lues were held responsible for the Raynaud's symptom complex, for the damage was already beyond repair when antiluetic treatment was begun. It is significant to note that an attack of local asphyxia of the fingers occurred April 7, although this attack was much briefer and milder than the previous ones.

DISCUSSION

To summarize, then, the case presents symmetrical gangrene of the feet, and four unquestioned attacks of local asphyxia of the fingers, without exposure to unusual cold. The transient nature of the glycosuria rules out diabetes as the etiologic factor. A gonorrheal vaginitis with probable arthritis occurred, and a gonorrheal septicemia with emboli might be held responsible for the gangrene of the lower extremities, but the question of such sepsis was never proved and does not seem probable clinically. The patient had congenital syphilis, and an obliterative endarteritis could cause the condition. But the vasomotor attacks of the fingers, combined with the symmetrical gangrene of the feet is so typical of Raynaud's disease that the latter diagnosis must be very seriously considered. In fact it seems justifiable to conclude that the patient simultaneously suffered from three diseases—gonorrheal vaginitis with arthritis, congenital syphilis and Raynaud's disease. It remains to discuss what relation, if any, existed between these maladies. Were we dealing with a pure time coincidence, a simultaneous occurrence without interdependence, or did the syphilis, or the gonorrhea, or both, act in relation to the Raynaud's symptoms as the "*Auslosendes Moment*?"

It is not within the scope of this paper to include more than a brief summary of the literature. A complete bibliography of those publications which specifically consider the relation between syphilis and Raynaud's disease has been added for those more fully interested. Raynaud's disease is uncommon, yet its occurrence is not so extremely infrequent as to relegate it to the category of medical rarities. Cassier saw 56 cases, and including a careful review of the literature up to 1911, has gathered together over 300 unquestioned instances of the disease. Coming now to the group of cases in which an hereditary or acquired lues is present, we find a considerable discrepancy in the figures published. Monro would allow only 2.8 per cent, while Castellino and Cardí find 22 cases of syphilis in 306 cases of Raynaud's disease. Probably the proportion is still higher. The appended 54 references contain more than 22 cases. Perhaps 10 per cent will not be too high an estimate.

Raynaud himself seemed not to attach any importance to the presence of syphilis, though he mentions an observation to that effect by Portal (1836) and Henry (1857). Defranc notes an early record of this combination described by Liston in 1836, before Raynaud had written his treatise. As Cassirer correctly points out, Morgan in 1889 was probably the first to direct attention to the possible interdependence of syphilis and Raynaud's disease. Cases illustrating this coincidence in acquired lues, have been reported by Amann, Klotz, Morgan, Castellino and Cardì, Elsenberg, Fordyce, Giovanni, Germer, Jacoby, Morton, Nash, Ornellas, Puzey, Riva, Tounton, Balzer and Fouquet, Lustgarten, Cassirer, Phelps, Schuster, Gaucher, Gougerot and Meaux Saint Mare, and Semon. To these must be added those cases of congenital lues, exhibiting a Raynaud's symptom complex, namely, the reports of Hutchinson, Marsh, Humphrey, Krusowski, Young, Wherry, Dyce Duckworth, Pasteur, Rietschel, Schiff, Spieler, Stoltzner, Glaser, Brocq (quoted by Gaucher), Bosanyi, Durantes, Beck, and the case that forms the basis of this report.

As regards the pathologic anatomy of Raynaud's disease, Dehio's statement in 1893 obtains today, namely, that none of the published pathologic investigations, where negative findings have been reported, are complete and detailed enough to justify the conclusion that this malady has no recognizable lesions. The positive findings include changes in the nervous system and circulatory system, either separately or in both. But such changes have been very inconstant, and their etiologic relationship to the Raynaud's disease rather indefinite, while the majority of cases autopsied have failed to reveal any lesions whatsoever. The theories as to the pathogenesis of the disease are briefly

THEORIES AS TO PATHOGENESIS

1 The theory of Raynaud himself. He would classify the syndrome as a central vasomotor neurosis, due to direct or reflex stimuli on the vasomotor center. The majority of writers agree in this conception, modifying it only in certain details.

2 There are those (Pitres and Noesske, etc.) who insist that a peripheral neuritis is the cause of the disease.

3 In disease of the peripheral arteries some have found their etiologic agent.

4 Concerning a case of acquired lues with Raynaud's disease, Gaucher, Gougerot and Meaux Saint Mare offer the following explanation. Either vascular spasm, caused by a syphilitic peripheral neuritis or a central vasomotor disturbance, as the primary feature, a secondary endarteritis from prolonged vasoconstriction sufficing to complete the clinical picture, or more probably, a primary luetic endarteritis remain-



Appearance of gangrenous foot in author's case

ing latent symptomatically until a spasm set up through the nerve channels determines the onset of local asphyxia and subsequent gangrene

5 Some authors (Hochenegg, Fuchs) find it necessary to assume a special as yet unknown trophic center, through disease of which or the nerves leading from which, Raynaud's symptom complex follows

6 Bearing syringomyelia in mind, some are tempted to seek a similar origin, in the spinal cord for Raynaud's disease (Bender, Tscherback, Lyle and Grieve) Oppenheim would suggest that a group of cases at least are due to lesions of the posterior and lateral columns

7 Still others (Moebius, Solis-Cohen, Levi, Rothschild) ascribe a causal rôle to the glands of internal secretion, especially the thyroid

It is worth noting that Raynaud's symptom complex has been observed as a complication in some fifty different diseases, including acute and chronic infectious diseases, intoxications, mental and nervous maladies, disorders of the circulatory system and ductless glands, etc. These widely divergent types of disease cannot all be responsible for the unique and singular syndrome of Raynaud. This very fact is one of the most suggestive arguments in support of its being a clinical entity. That Raynaud's disease (probably 10 per cent of all cases) occurs very frequently in syphilitic patients, might superficially suggest an intimate relationship. However, this statistical preponderance is not surprising, in view of the prevalence of syphilis. A similar case might be made out for tuberculosis. This frequency, then, can have no weight in establishing any relationship between the two diseases.

In discussing the coincidence of these diseases, we can suppose the following possibilities

1 The symmetrical gangrene and, more important, the other signs and symptoms, may be caused directly by a syphilitic lesion of blood vessels or the nerve supply to such blood vessels. For the final proof of such a contention, the *Spirochaeta pallida* must be demonstrated in the lesion, just as the gonococcus has been found in the tissues of a gonorrheal arthritis, or the spirochete by Noguchi in the cords of tabetics and brains of paretics. Probably many cases of myocardial weakness were suspected of a luetic origin, even though no gummatous process was histologically discernible, but positive statement of fact had to await Warthin's demonstration of the spirochete in the heart muscle.

2 Raynaud's symptom complex may be caused indirectly by the syphilitic toxin. The number of conditions in which this toxin is the etiologic agent are becoming increasingly appreciated. We are coming to recognize a larger number of arthropathies as luetic, even though

the histology is not characteristically syphilitic, nor the signs and symptoms sufficiently typical to permit invariably of a correct diagnosis. Clinicians are becoming convinced that lues of the lung is not as rare as hitherto supposed. We have come to regard an aortitis confined to the arch of the aorta as almost always luetic, even though no gummatous change is present at necropsy. In the conditions mentioned, the history of syphilitic infection, the Wassermann reaction and the response to specific therapy have been the basis for the diagnosis. To what extent do these standards apply to the combination, lues and Raynaud's disease? Some cases of Raynaud's disease have been ascribed to a luetic basis, merely because of a positive Wassermann or history. This is quite unjustifiable. The positive Wassermann and history merely indicated that the patient had syphilis, but not that the Raynaud's disease was an expression of active syphilis.

Those who defend an interdependence between the two diseases advance as their strongest argument, the disappearance of the Raynaud's signs and symptoms under vigorous specific medication. Some of the most striking instances are those reported by Kisowski, Morgan and Bosanyi. Naturally such cases are extremely suggestive, but are they conclusive? It would seem preposterous to doubt such evidence, and yet when one recalls how suddenly and without warning a local asphyxia or local syncope may disappear, a certain skepticism may be permitted as to the rôle played by the specific therapy. In those cases in which local syncope and asphyxia never occurred, and merely a symmetrical gangrene was favorably influenced by mercury or salvarsan, we may actually question the diagnosis of Raynaud's disease and wonder whether a specific endarteritis was not the pathologic basis of the gangrene.

3 We may suppose that syphilis may so lower the bodily resistance as indirectly to make the individual more susceptible to Raynaud's disease. If this were the only relation between the two diseases it would be the same and no more important than the influence of the many other acute and chronic infectious diseases, intoxications, etc., in which Raynaud's syndrome has been observed as a complication.

Morgan concludes concerning his case "that Raynaud's symptoms appeared as manifestations of tertiary syphilis." Bosanyi concludes similarly concerning his two cases "Raynaud's disease can develop as a symptom of hereditary lues." But the final proof of such a point of view is still lacking.

It is a pleasure to acknowledge the kindness of Professor Dock in permitting me to report this case.

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A STUDY OF ATRIOVENTRICULAR RHYTHM FOLLOWING AURICULAR FLUTTER *

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A cardiac rhythm arising in the atrioventricular junctional tissues in the human is a rare and usually very transient affection, so uncommon in fact that it has never been the object of careful investigation. Premature beats and paroxysms of tachycardia having their origin in the junctional tissues have been reported frequently. Belski¹ in 1909 wrote of six cases of acute infectious disease in which polygrams seemed to indicate that the bradycardia was not infrequently due to an atrioventricular rhythm. In one case the subcutaneous injection of atropin sulphate, gram 0.001, produced in twenty minutes an acceleration of the pulse from 42 to 137, while the rhythm apparently changed from one arising in the atrioventricular junctional tissues to one of the normal sino-auricular type. Five hours after the atropin had been given the pulse had dropped to 55 and the rhythm was still normal. The next day at a rate of 46 the polygram again showed atrioventricular rhythm.

Williams and James² reported in 1914 a patient showing a reversal of the cardiac mechanism in whom atropin produced no change. In October, 1913, Hume,³ writing on the polygraphic study of four cases of diphtheria, discussed two cases which seemed to show atrioventricular rhythm for a few days just preceding auricular flutter and death. In one of these the pulse rate during the *a-v* rhythm was high (98 to 100), in the other 68. In the latter case the sino-auricular node examined postmortem was inflamed and the muscle fibers were in a state of granular degeneration while the node of Tawara and the bundle of His were almost normal.

Experimentally atrioventricular rhythm in the animal's heart has been produced and studied by several investigators, notably by Thomas Lewis.⁴ He has shown that when the sino-auricular node is destroyed

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1 Belski, A. Ztschr f klin Med, lxxvii, 1909

2 Williams, H. B., and James, H. Heart, 1914, v

3 Hume, W. E. Heart, 1913, v

4 Lewis, Th. Heart, 1913-1914, v

or sufficiently depressed by cold or vagal stimulation, the atrioventricular node assumes the rôle of pace-maker for the heart. Its automatic rate is lower than that of the sino-auricular node, but higher than that of the lower levels of the atrioventricular bundle as found at times in complete heart block. A rapid rhythm arising in the atrioventricular junctional tissues as in some cases of paroxysmal tachycardia is probably due to irritation and not to the normal rate of stimulus production in this area of the heart.

Experimentally one may find in atrioventricular rhythm that the intervals between auricular systole and ventricular systole vary from a positive value shortened below that of normal rhythm to a negative value, depending partly on the site of the stimulus production in the junctional tissue and partly on the resistance to conduction between (a) node and ventricle and (b) node and auricle. If the pacemaker lies low in the node there may presumably be a definite interval between ventricular systole and auricular systole—i. e. a negative *as-vs* value (Fig. 21). Or if the auriculonodal junction is abnormally resistant to the passage of impulses, the negative *as-vs* interval may presumably occur even with the pacemaker in the central part of the atrioventricular node. Lewis, White and Meakins⁵ have shown experimentally that in the cat the auriculonodal junction is the most susceptible point of the *a-v* conducting system when asphyxiation is used as the test-method.

Since by the electrocardiogram *P* represents auricular systole and *R* the onset of ventricular systole, we may have in atrioventricular rhythm values varying from shortened *P-R* intervals to definite *R-P* intervals. In a similar way venous tracings would show conduction intervals varying from shortened *a-c* intervals to those of a *c-a* sequence.

The present case which I report is exceptional for the following reasons:

First, the patient was suffering from an auricular flutter with a ventricular rate of 130, with no discomfort other than slight dyspnea on exertion and with no realization that there was anything at all wrong with his heart.

Secondly, instead of returning to a sino-auricular rhythm following the fibrillation of the auricles, which is the frequent story of the course of the "flutter heart" under treatment, this patient underwent a transition from fibrillation to a rhythm arising in the atrioventricular junctional tissues.

5 Lewis, Th., White, P. D., and Meakins, J. Heart, 1914, v

Thrdly, this atrioventricular rhythm has established itself so well that it presents an excellent opportunity for study⁶

Details follow

History—W S, a single man of 37 years, a teacher, entered the nerve service of the Massachusetts General Hospital under the charge of Dr E W Taylor on Jan 8, 1915. He came for the relief of "weakness in his legs" and "obesity." His admission diagnosis was "tabes" (?)

Family and Past History—Father, aged 71, confined in a hospital for the insane. Mother, one brother and two sisters living and well. Two sisters dead—diphtheria and pneumonia. Patient has had pertussis and rarely a sore throat. Never rheumatism or chorea. Severe attack of typhoid fever with relapse nineteen years ago. Right ankle sprained at age of 9 years. Patient was always stocky and stout and played football in youth. After typhoid fever nineteen years previously his legs became much smaller and his weight "settled in his abdomen."

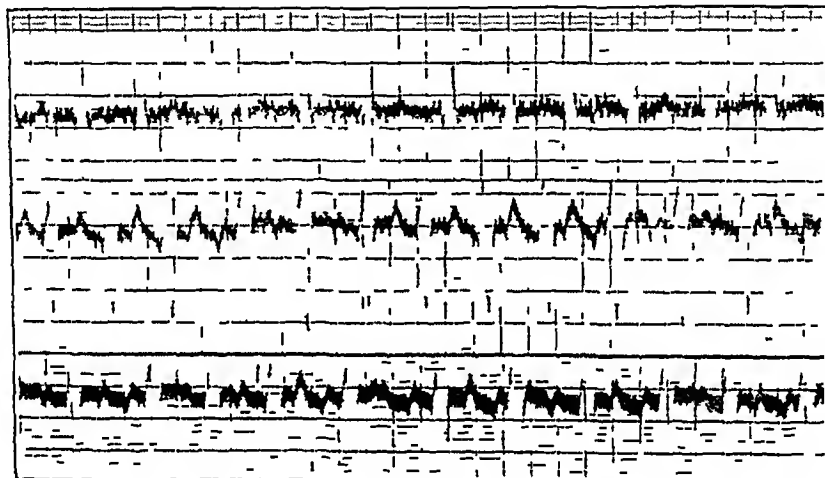


Fig 1—Electrocardiogram showing the three leads of Einthoven in auricular flutter with rapid ventricular action. Taken Jan 10, 1915. In this as in the remaining electrocardiograms the ordinate represents 10^4 volt. Abscissa represents time interval of 0.2 second. Curves in this and following illustrations reduced to two-thirds size of originals.

History of Present Complaint—About nine years previously patient noticed gradual onset of weakness in his right knee and ankle. He would often get tired on walking but in 1907 he climbed a height of 2,800 feet in Maine without discomfort. For the past three years he has fallen down about once a month, due to his "knee giving out." No dizziness, nausea, vomiting or headache. He has been unable to carry anything heavy for years—cannot now

6 April 12, 1915, the rhythm was continuing unchanged, ten weeks after its onset. He was examined frequently in this period. May 11, 1915, the patient again showed auricular flutter by electrocardiogram, with an auricular rate of 300 and an irregular ventricular response at a rate of 100 per minute. The patient observed a sudden change in his pulse from a slow, regular rate to an irregular and much more rapid rate on the 10th of May, the day before the electrocardiogram above noted was taken, and fourteen weeks after the onset of the atrioventricular rhythm. May 18 an electrocardiogram showed again the atrioventricular rhythm restored through the administration of 18 grams of digitalis leaves in the course of a week. A bigeminy similar to that previously described was present.

carry a suitcase He has great trouble going up and down stairs—his knees fail to support him and he has to pull himself up by the hand rail No loss of sphincteric control For several years some dyspnea on exertion, ascribed by patient to his obesity No cough or expectoration No edema

Habits Tobacco four to five cigarettes daily, an occasional pipe No alcohol Venereal diseases denied

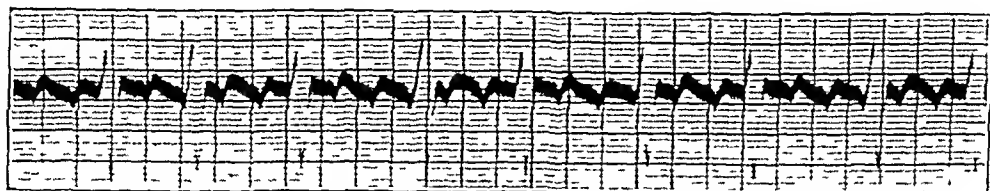


Fig 2—Electrocardiogram Lead II Auricular flutter

Physical Examination—Hair scanty, but a moderate amount occurs on the body (axillae, chest, abdomen, pubes) Mucous membranes of good color Pupils slightly irregular but react normally Tongue protruded straight and shows no tremor No lead line on gums Tonsils not enlarged

Lungs showed slight dullness at left apex front and back with prolonged expiration No râles Spine straight, not tender

Heart Accurate percussion impossible because of thick chest wall but heart seems somewhat enlarged Apex not felt No murmurs Sounds of fair quality Rhythm at times irregular

Abdomen obese, otherwise normal Liver not enlarged to percussion or palpation Genitalia normal

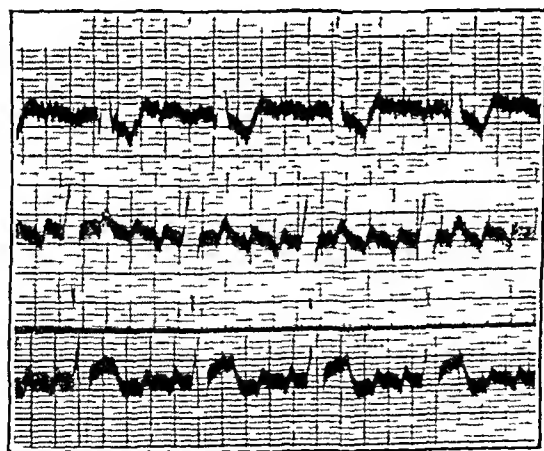


Fig 3—Leads I II and III Auricular flutter with 4:1 a-v block Taken Jan 18, 1915

Extremities show muscular weakness

Reflexes Right knee-jerk not obtained, left weak No ankle-clonus, Babinski or Oppenheim Romberg's sign absent Abdominal and cremasteric reflexes normal Arm reflexes not obtained

Gait "Slaps feet down and is hesitant, not ataxic"

Clinical Observations—Temperature as a rule subnormal (never above 99 F while in the ward) Respiration 20 to 24 Pulse rate at wrist dropped steadily from 120 on entrance to 38 on discharge (nineteen days later)

Blood pressure 125 mm Hg, systolic, 92 mm Hg, diastolic

Urine Ounces 20 to 55 daily Two examinations showed a clear acid urine of 1022 gravity without albumin, sugar, bile or acetone bodies, rare hyaline cast in the twenty-four-hour sediment

Blood White cells = 6,300 per c mm Red cells = 4,240,000 per c mm
Hgb = 85 per cent Smear normal Wassermann test negative

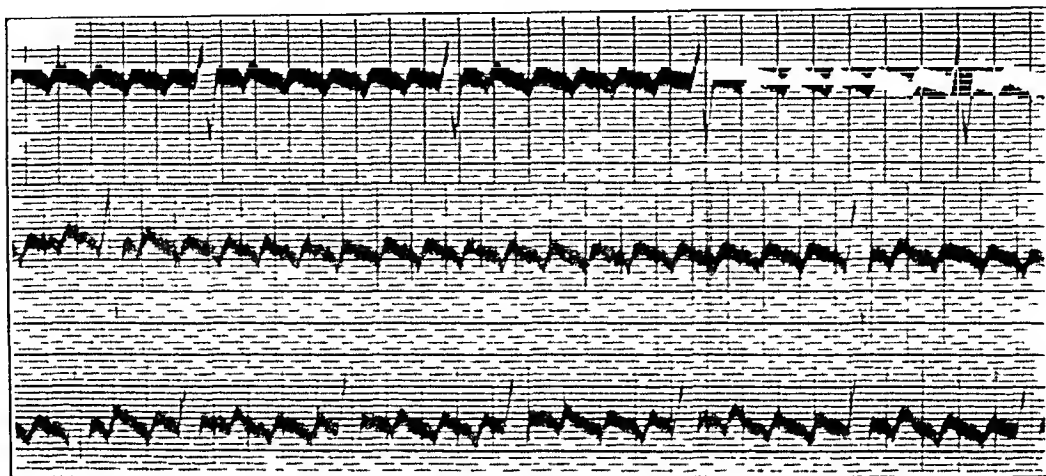


Fig 4—Lead II with right vagal pressure Upper and middle curves represent effect of vagal pressure, 6 l and 18 l block, respectively Lower curve shows the electrocardiogram following the vagal pressure

Roentgen-Ray Examination—January 11 Skull, "medium sized sella turcica with apparent bridging of clinoids" January 22 (Chest at 7 feet from tube) "Apex of heart is in the sixth interspace, 11.5 cm to left of median line Right border is 6.4 cm to right of median line Total transverse diameter is 17.9 cm Greatest transverse diameter of great vessels 8 cm Length of heart 18 cm"

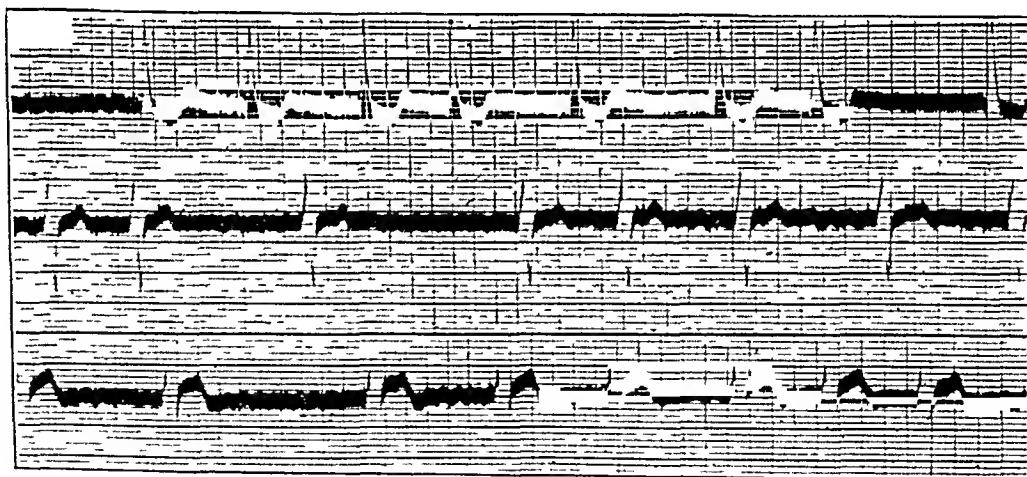


Fig 5—Leads I, II and III Auricular fibrillation Taken Jan 19, 1915

Weight fell from 183 to 177¼ pounds on a fat-free diet Fields of vision normal Two attempts to have the patient take levulose for a tolerance test were unsuccessful on account of vomiting

Drugs—Aside from one dose of morphin solution on January 8, no drugs were given other than pills of Caesar and Loretz digitalis leaves, gram 01, t i d for eight days, the patient receiving 24 grams from January 12 to 19, inclusive Patient was discharged Jan 27, 1915, nineteen days after entrance

Electrocardiograms—The Cambridge model of the Einthoven string galvanometer with rotary time-marker was used

January 9, the day after the patient's admission to the hospital, the irregularity of the pulse was brought to my attention. A radial pulse tracing taken then showed that flutter of the auricles was probably present. The next day, January 10, the first electrocardiogram was taken and the series of plates showed that auricular flutter was in progress (Figs 1 and 2). Also there is indica-

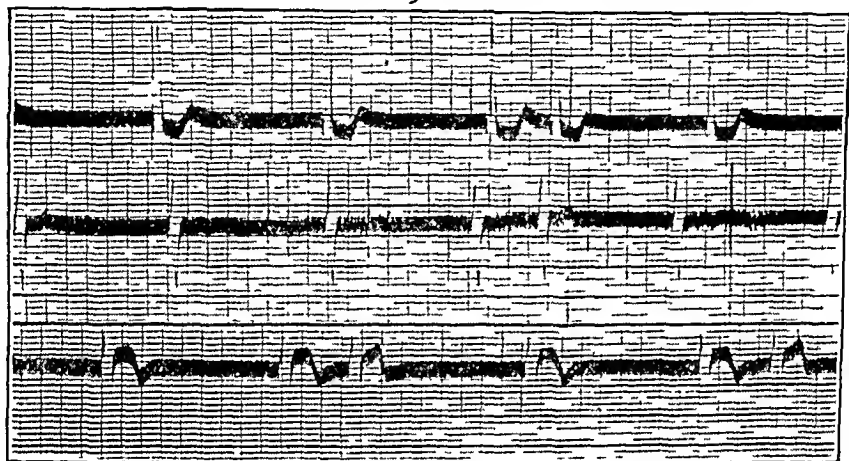


Fig 6—Leads I, II and III. No evidence of auricular activity. Taken in a m, Jan 23, 1915. Ventricular rate = 43 per minute.

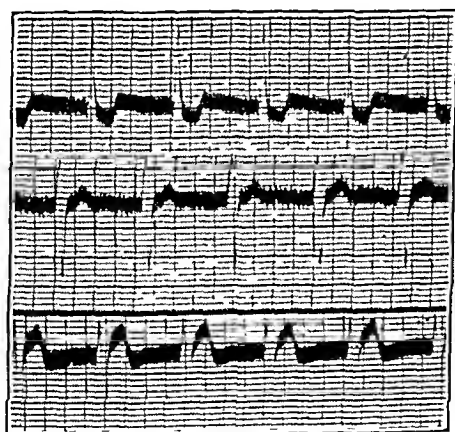


Fig 7—Leads I, II and III. No evidence of auricular action. Taken in p m, Jan 23, 1915, same day as that on which the record shown in Fig 6 was obtained. Rate much higher, 70 per minute.

tion from Leads I and III and from the width of the ventricular complex that conduction in the right branch of the *a-v* bundle is defective. The auricular rate varied from 285 to 292 on January 10, on the 15th it was 250 to 252, on the 16th 272 and on the 18th 244, a range of 47 contractions per minute. The ventricular rate dropped from 130 on the 10th to 96 on the 11th, 67 on the 15th, and 61 on the 18th. At this latter rate there was a clear 4:1 *a-v* block (Fig 3). At the higher rates the degrees of block were irregular. Vagal pressure (especially on the right side) increased the block definitely, on the

15th of January producing a pause in the pulse of over four seconds and equivalent to an 18 1 block (Fig 4)

On January 19 auricular fibrillation was discovered (Fig 5) The ventricular rate was 50 and irregular The electrocardiographic oscillations representing the fibrillation of the auricles occurred at about the rate of 450 per minute The next day the condition persisted but the oscillations were smaller The

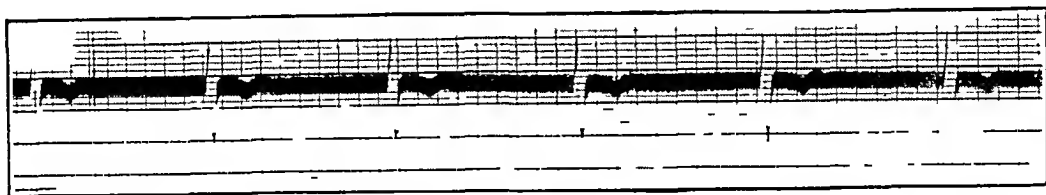


Fig 8—Lead II No evidence of auricular action Taken Jan 25, 1915

ventricular rate then was 38 to 40 On January 23, three days later, the ventricular rate was 43, in general much more regular, at times bigeminal, while the diastolic portion of the electrocardiogram was almost smooth (Fig 6) On the afternoon of the same day the electrocardiogram showed a rate of 70 (Fig 7), the ventricular complexes almost equidistant, varying at times only a few thousandths of a second, there was no sign of auricular systole The condition at this time may have been one of idioventricular rhythm without auricular contraction (either because of a very fine auricular fibrillation or of a total standstill of the auricle) or there may have been at this time an atrio-ventricular rhythm with the auricular complex concealed somewhere in the ventricular The fine oscillations in the first and second leads are due to the patient's tremor, which in the third lead has almost disappeared

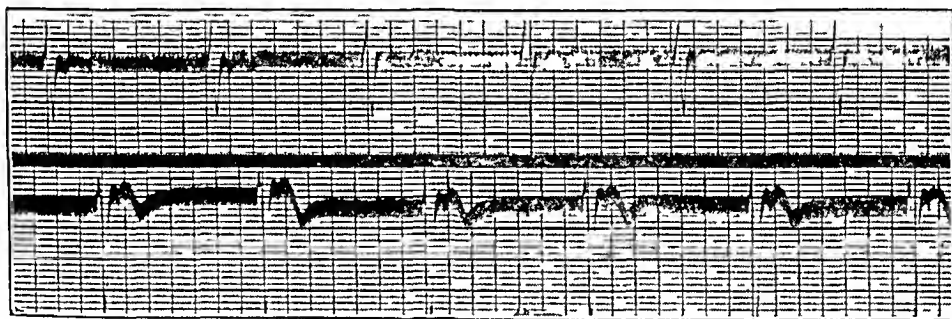


Fig 9—Leads II and III, First evidence of invert auricular complex following the initial ventricular complex Taken Jan 30, 1915

January 25, two days later, the same situation occurred, there being direct evidence of a regular ventricle systole only (Fig 8) Inversion of the I deflections appeared here for the first time The intervals between ventricular complexes on the electrocardiogram vary less than two-hundredths of a second Diastole is smooth

On January 30 a new feature appeared in the electrocardiogram, an inverted deflection immediately after the S and preceding the T (Fig 9) This deflection is interpreted as the index of auricular systole It appears most distinctly in Leads II and III The reasons for considering that this is the auricular complex are as follows (a) the deflection appears in an inverted form at a brief interval after the regularly occurring R wave and is represented by a definite wave in the jugular pulse (Figs 19 and 20), (b) it is subject to certain conditions to be mentioned below, and (c) there is no other evidence in systole or diastole of auricular action Williams and James² by means of the fluoroscope

were able to see the contraction of the auricle in their case of "Reversal of the Cardiac Mechanism," although it was impossible to time its contraction in relation to the ventricular beat. In the present instance, with the help of Dr George W Holmes, a similar examination was made and the auricle and ventricle seemed to contract synchronously

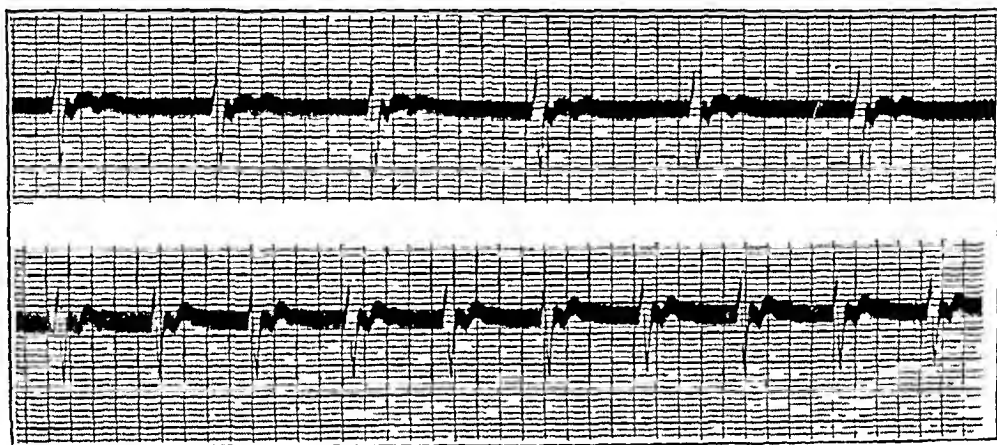


Fig 10 Lead II Showing the effect of atropin, gram 0.002 injected subcutaneously. Upper record taken before the injection, lower record taken sixty minutes after the injection. Rate increased from 42 to 66. Note the change of the T wave after atropin. Taken Feb 10, 1915

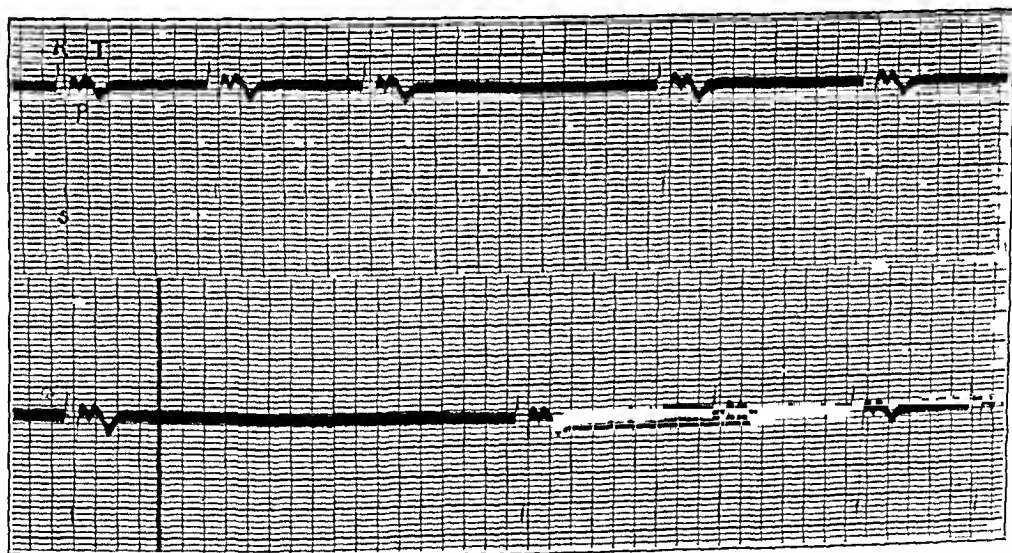


Fig 11—Lead III Showing the effect of right vagal pressure. In upper curve pressure was begun shortly after second beat, in lower curve pressure was begun when the plate began to travel

The fact that the ventricular complex has not changed from its character while responding to auricle except with regard to the T deflection, makes it evident that there persists here a supraventricular rhythm which is not induced by auricular systole. If the excitatory process does not arise in the ventricular musculature or in the auricles it must have its origin in the atrioventricular junctional tissues perhaps as low as the left branch of the *a-v* bundle. The reversal of the interval *as-vs* to *vs-as* would indicate that the excitatory process arising

somewhere in the *a-v* junctional tissues and traveling down to the ventricles and up to the auricles reaches the former first either because of the distal position of the pacemaker in the *a-v* tissue or because of the resistance in the auriculonodal junction, or from both causes (Fig 21) To test this a further course of digitalis, 2 gm of the leaves in one week, was given while the patient was showing the atrioventricular rhythm Except for a slight lengthening of the *R-P* interval there was no change after 1 gm, but on the completion of 2 gm the electrocardiogram showed no longer any definite auricular deflection A condition of backward block from the *a-v* node affords a likely explanation of this phenomenon, the *P* being absent or buried in the *T* (Fig 13) Experimentally the auriculonodal junction has been shown to be the susceptible joint in *a-v* conduction as mentioned above

In this case the considerable variation in the length of the *R-P* interval (from 0.123 to 0.420 sec) under different conditions, with regularly recurring ventricular contractions, is evidence here against a mechanical origin of the auricular complex resulting from the ventricular contraction such as has been suggested by Cohn and Fraser⁷ in their case of block in which frequently inverted auricular complexes followed directly on the ventricular

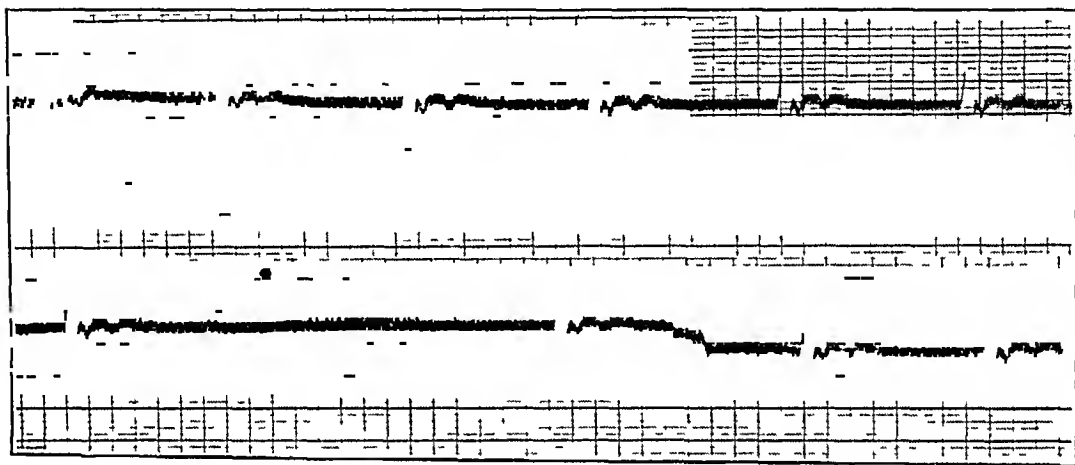


Fig 12—Lead II Showing the effect of left vagal pressure Upper record taken before the vagal pressure, lower record during the vagal pressure Taken Feb 15, 1915

INFLUENCE OF VARIOUS FACTORS ON THE ATRIOVENTRICULAR RHYTHM

Rate—Daily variation The table of pulse rates shows well the daily variation of the pulse, which was slow in the morning just before breakfast, and usually more rapid after the evening meal This variation accords in general with that seen in sino-auricular rhythm The one occasion (Feb 27, 1915) on which the morning rate was 72 was apparently due to the fact that the preceding night had been badly interrupted by vomiting and abdominal distress After spending the day in bed the pulse dropped to 44 The average morning and evening pulse rates for fifty-five days were 40 and 45, respectively It should be noted that the patient lives quite comfortably with his atrioventricular rhythm and is up and about every day

⁷ Cohn, A E, and Fraser, F R Heart, 1914 v

Exercise Exercise increased the rate Repeated lifting of the arms produced a quickening amounting to but a few beats while the exertion of climbing one flight of stairs increased the rate from 32 to 57 in one instance, and from 46 to 54 on another occasion, the pulse keeping perfectly regular After resting one half hour following further exercise (walking about) on the first occasion the rate became 42

TABLE OF PULSE RATES

1915	a m	p m	1915	a m	p m
1/25	38	46	3/13	40	48
1/26	38	44	3/14	42	42
1/27	38		3/15	36	44
1/30		43	3/16	38	40
2/ 6		47	3/17	50	52
2/10		42	3/18	40	38
2/11	34	52	3/19	42	34
2/12	32	50	3/20	44	36
2/13	32	50	3/21	36	40
2/14	37	46	3/22	38	36
2/15 [*]	32	58	3/23	38	42
2/16	32	45	3/24	32	50
2/17		58	3/25	36	48
2/18	42	46	3/26	36	54
2/19	46	50	3/27	50	46
2/20	46	48	3/28	42	42
2/21	36	50	3/29	38	42
2/22 [†]	32	44	3/30		50
2/23	58	50	3/31	36	50
2/24	38	56	4/ 1	44	48
2/25	54	46	4/ 2		44
2/27	72	44	4/ 3	46	54
2/28	44	46	4/ 4	34	40
3/ 1	38	45	4/ 5	36	42
3/ 5	40	48	4/ 6	48	40
3/ 6	46	58	4/ 7	38	48
3/ 7	46	40	4/ 8	36	44
3/ 8	34	36	4/ 9	36	34
3/ 9	32	46	4/10	36	40
3/10	34	40	4/11	40	40
3/11	48	44	4/12	40	
3/12	36	50			

^{*} Digitalis started [†] Digitalis stopped

Respiration Quiet respiration had very little effect on the rate of the atrioventricular rhythm, but forced respiration produced definite results, corresponding to the respiratory arrhythmia of the normally beating heart These observations were made with the Mackenzie ink polygraph The rates during four periods of forced expiration were 42, 43, 43, and 41 beats per minute, while during the periods of forced inspiration preceding the periods of forced expiration, the rates were 48, 52, 55 and 50, respectively—an average of 42 beats per minute during forced expiration and of 51 beats per minute during forced inspiration

Atropin sulphate injected subcutaneously in the dose of 0.002 gram did not restore sino-auricular rhythm. It was thought that the sino-auricular node might have been depressed by vagal influences (as had probably happened in Belski's case) but such was not the situation. The atrioventricular rate, however, responded to the withdrawal of the vagal influences (Fig 10), and in fifteen minutes rose from a regular rate of 42 to one of 68. The high point was thirty minutes after the injection when the electrocardiogram showed a rate of 71. Thereafter the rate gradually dropped, and next morning registered 34.

Vagal pressure produced marked decrease in the rate of the heart during its atrioventricular rhythm, moderate right sided pressure slowing the heart from a rate of 50, so that at one time a pause of over

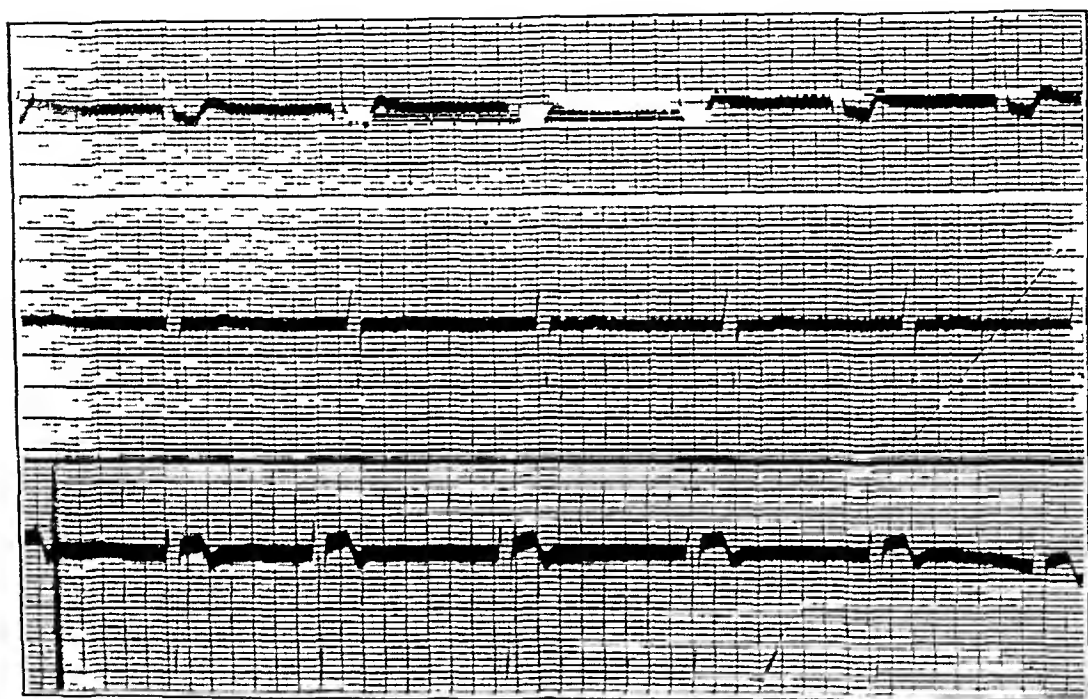


Fig 13—Leads I, II and III Showing the effect of 2 grams of digitalis leaves in one week. Taken Feb 23, 1915

four seconds occurred (Fig 11). The left vagus acted in the same way on moderate pressure, the heart which was beating at 37 stopping for over four seconds (Fig 12). Ocular pressure was tried on both sides but the results were less striking than in the case of vagal pressure. The ocular pressure was not exerted strongly enough to cause severe pain. Experimentally Lewis⁸ found that the right vagus appears to have a larger control upon *a-v* rhythm than does the left, but in some animals he found the reverse true. In the present case, so far as can be judged with regard to rate, both vagi acted similarly. Lewis' conclusion that the influence of both vagi is usually more pro-

⁸ Lewis, Th. Heart, 1914, v

found, relatively and absolutely on the *a-v* rhythm than on the *s-a* rhythm, finds indirect confirmation in the human subject here, for although there has been no sino-auricular rhythm to test in this patient, I have not seen any person with normal rhythm not under the influence of digitalis who responded so readily to slight vagal pressure as did this individual. The fact that the sino-auricular node did not escape during the marked slowing of the atrioventricular rhythm in this patient by vagal pressure would suggest that this node had ceased to function.

Digitalis This drug, in a dosage of 2 gm of the leaves during the period of one week, had practically no effect on the rate of the atrio-

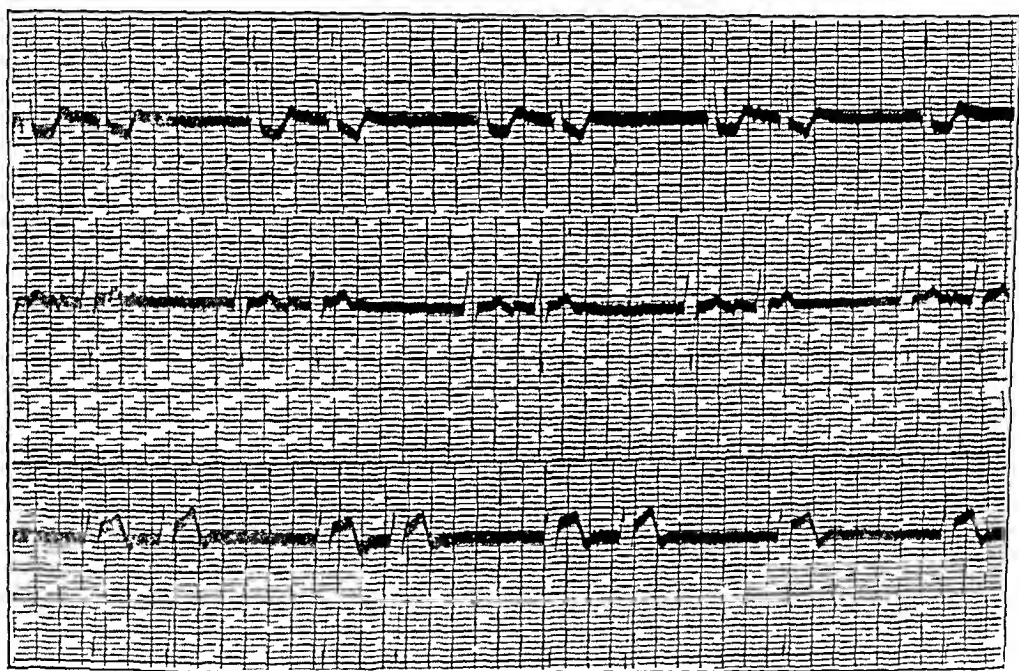


Fig 14—Leads I, II and III Showing the bigeminy present on Feb 24, 1915, two days after stopping digitalis Before injection of atropin

ventricular rhythm (Fig 13), although a bigeminy occasionally appeared after it had been taken. The day after the last of the digitalis was administered the ventricles were beating regularly at a rate of 38 without any clear evidence of auricular complex in the electrocardiogram (Fig 13). The next day the auricular deflection reappeared and a bigeminal pulse occurred (Fig 14). Atropin (0.002 gm) was injected subcutaneously, an acceleration of the pulse to 80 followed three hours later (Fig 16). It was thought that in this way the auriculonodal block might be released. The *R-P* interval became definitely shorter and the bigeminy constant at first (Fig 15), but later when the rate was fixed at 80 the auricular complexes disap-

peared. An electrocardiogram taken at this time showed a remarkably uniform ventricular rate, the range in eight successive beats being but 0.007 second (from 0.748 to 0.755 second). Beside the retardation and disappearance of the auricular complex in the electrocardiogram, other evidence of toxicity from digitalis were headache and anorexia.

Variation of the R-P Interval—In order to determine this interval with some degree of accuracy the electrocardiographic plate was projected on a glass screen at a magnification of twenty-five times. Measurements of the various intervals were then made by means of calipers and a scale with divisions of $1/60$ inch. Comparison of the interval measurements was made with the measurements of the fifths

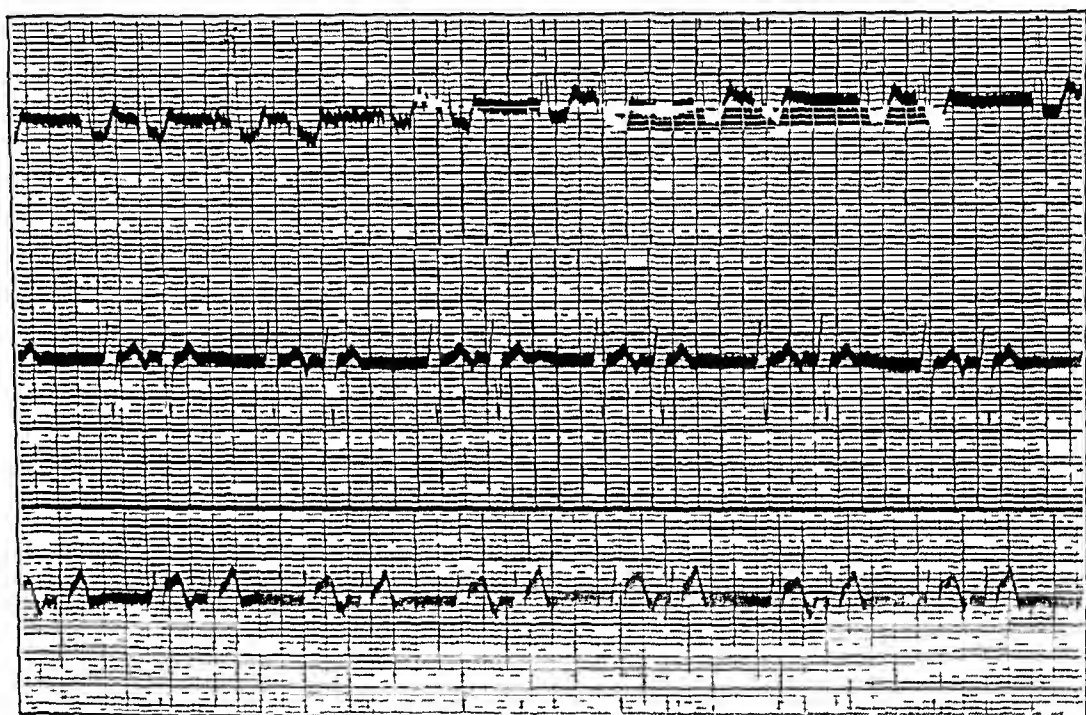


Fig. 15—Leads I, II and III. Bigeminy still present one and one-half hours after subcutaneous injection of atropin, gram 0.002, Feb. 24, 1915. Note increase in rate and decrease in R-P and P-R intervals.

of a second marked off by the vertical lines on the plate. In this way determinations could be made to thousandths of a second, the maximal range of one of the measurements itself done by three different individuals being 0.002 second. Taking all causes of inaccuracy into consideration I find that the maximal error amounts to less than one-hundredth of a second. The onset of the P deflection was often not sharp, but the notch itself was always clearly marked and quite uniform. Therefore, having determined the onset-to-notch interval in the most definite plate a correction was made on this basis from the notches found in the other plates measured.

The "normal" range of the *R-P* interval on different days was very considerable, from 0.123 second to 0.235 second, but from beat to beat the interval varies at the most but a few thousandths of a second when not influenced by some unusual factor

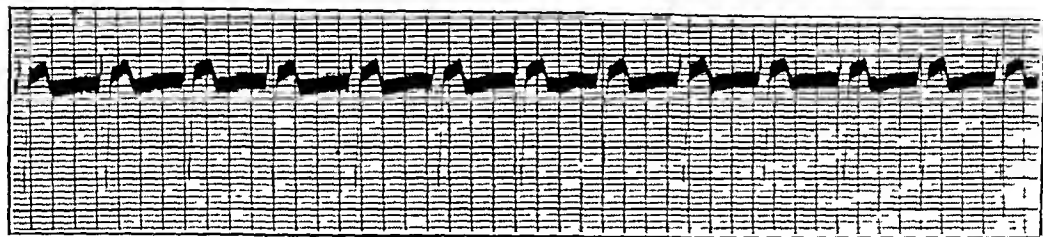


Fig 16—Lead III Taken three hours after atropin, Feb 24, 1915 Auricular complex no longer evident

Vagal pressure Pressure over the right vagus increased the *R-P* interval on one occasion from 0.143 second to 0.173 second and on another occasion from 0.231 to 0.253 second, the continuation of the pressure increasing the prolongation to 0.332 second coincident with

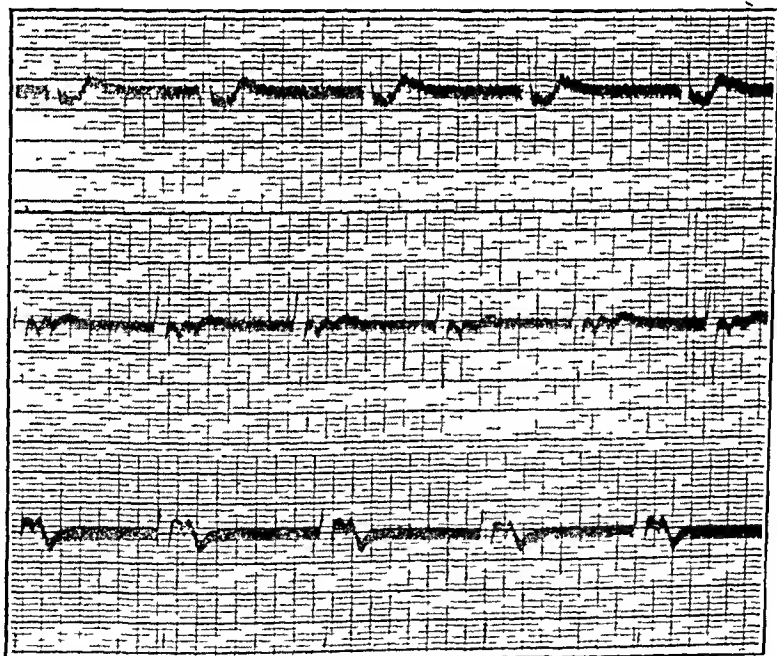


Fig 17—Leads I, II and III Taken March 1, 1915, one week after cessation of course of digitalis

a marked slowing of the whole heart On one occasion during left vagal pressure the *R-P* interval increased from 0.149 to 0.156 second

Digitalis After 1 gm of digitalis leaves the *R-P* interval measured 0.155 second, after 2 gm the *P* disappeared (Fig 13) Two days after stopping the digitalis the interval measured 0.378 to 0.420 second

(Fig 14), one week after the drug was omitted the interval was 0.217 second (Fig 17)

Atropin The sulphate injected subcutaneously in the dose of 0.002 gm when the *R-P* interval was 0.131 to 0.134 second caused a prolongation of the interval to 0.162 and 0.166 second (Fig 10) The explanation of this retardation is not clear It is probably due to the increasing difficulty of backward conduction with increase in rate (here the *a-v* rate rose from 42 to 71) Two days after stopping the digitalis atropin was again given, while the *R-P* interval was long (0.378 to 0.420), the interval was at first much shortened—nearly

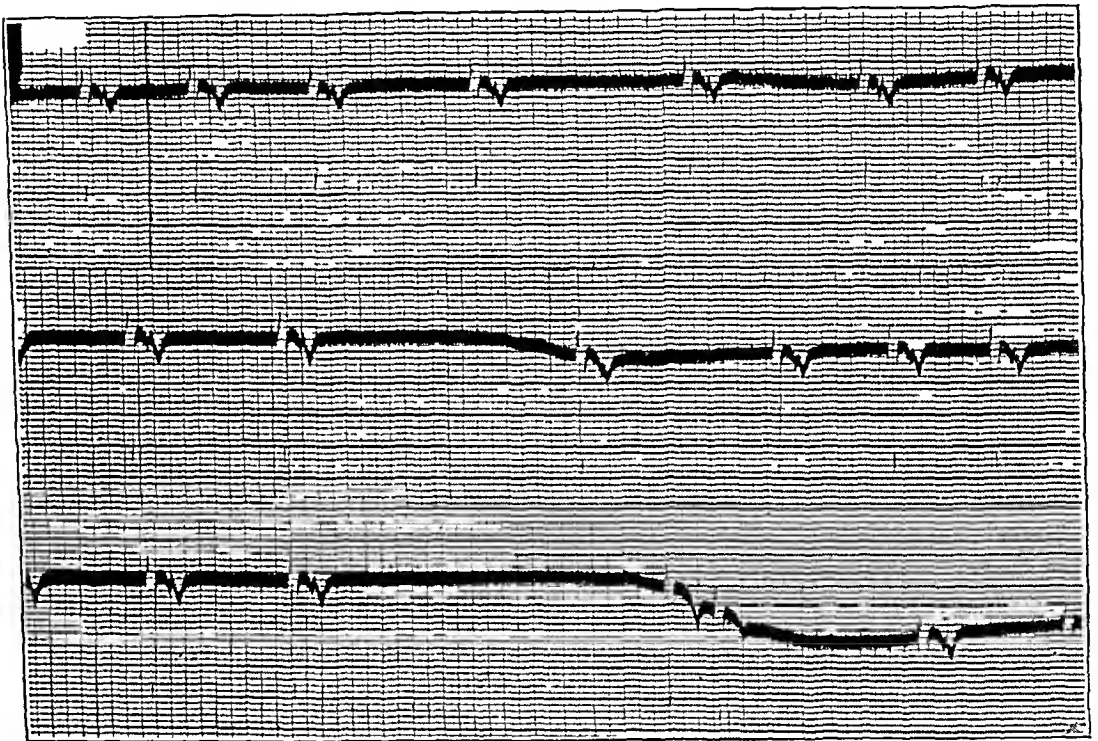


Fig 18—Lead III Showing in lowest record a coupled beat induced by the lengthening of the *R-P* interval by right vagal pressure Taken April 12, 1915

one-tenth of a second, to 0.320 second, with the continuation of the more rapid heart rate, however, the auricular deflections disappeared (Figs 14, 15, 16)

FURTHER OBSERVATIONS

Premature Beats—On three occasions premature beats were recorded electrocardiographically (one shown in Fig 19) Twice the premature contraction came at a time when a progressive slowing of the *a-v* rhythm was taking place; on the third occasion the beats prior to the premature beat were not recorded The site of the impulse formation in the case of the heterogenetic contractions seems to have

been the same in all three, since the shape of the complexes is identical, and since the *P-R* interval is fairly constant ($0.140 \pm$ second). It is obvious that these premature beats arise from a point proximal to the location of the *a-v* pacemaker, probably at or near the auricular end of the *a-v* junctional tissues as suggested by the invert character of the auricular complex and by the relatively short *as-vs* interval. The pause following the premature beat is not compensatory, in one case this returning ventricular cycle is longer than the initial ventricular cycle by one-fifth of a second (Fig 19), in a second instance they are equal, and on the third occasion there is no initial cycle for comparison, but the returning and first restored cycles are equal. In the

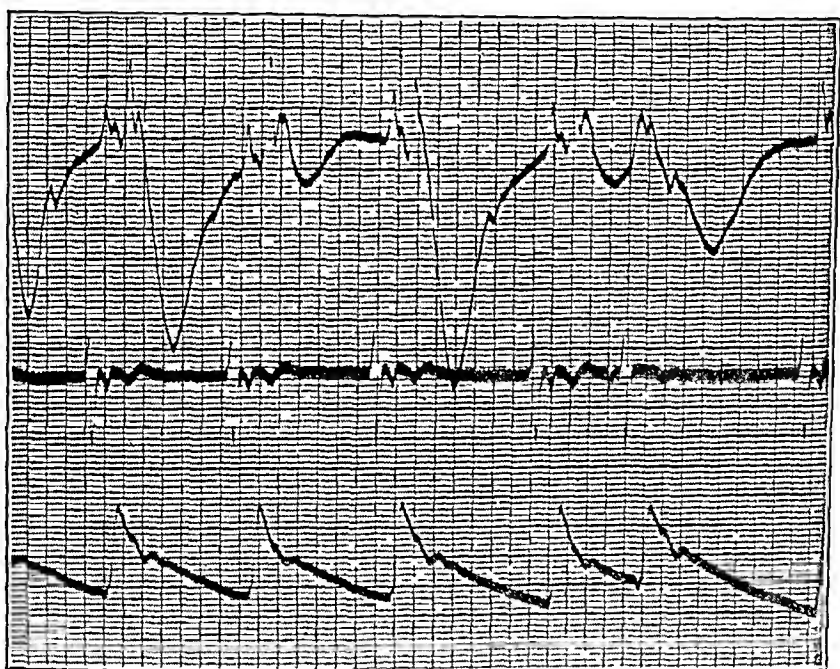


Fig 19—Polygram taken March 22, 1915, showing jugular pulse above, radial pulse below and Lead II of the electrocardiogram between. A premature beat interrupts the rhythm.

first two instances the *R-P* interval following the premature beat is of nearly the same length as are the *R-P* intervals preceding the premature beat (0.198 and 0.195 second as compared with 0.194 and 0.190 second, respectively).

Bigeminal Beats—Aside from the premature beats mentioned above coupling of the contractions has sometimes occurred during the course of the *a-v* rhythm and only when there has been prolongation of the *R-P* interval through the action of digitalis or of vagal pressure. The coupling consists of a sandwiching of an auricular contraction between two ventricular beats (Figs 14 and 18). In this sandwich the *P-R* interval has proved shorter than the *R-P* interval for

example, 0.240 second as compared with 0.378 second in one of the digitalis couples and 0.289 second as compared with 0.376 second in one of the vagal pressure couples. The mechanism of production of these paired beats is not clear. Several explanations are possible. Premature beats may be arising in the *a-v* pacemaker and resulting in ventricular response, while the auricles are cut off by "backward block," the increasing depression of the auriculo-nodal junction affording too great a resistance to the passage of the premature excitatory process. Another possibility, but less likely than the preceding one, is that the first beat of the pair consists of ventricular complex alone, the auricle being blocked off, while the second beat results from a premature contraction starting in some point proximal to the *a-v* pacemaker and reaching the auricle before it reaches the ventricle. Finally we may adopt the tentative suggestion of Lewis⁹

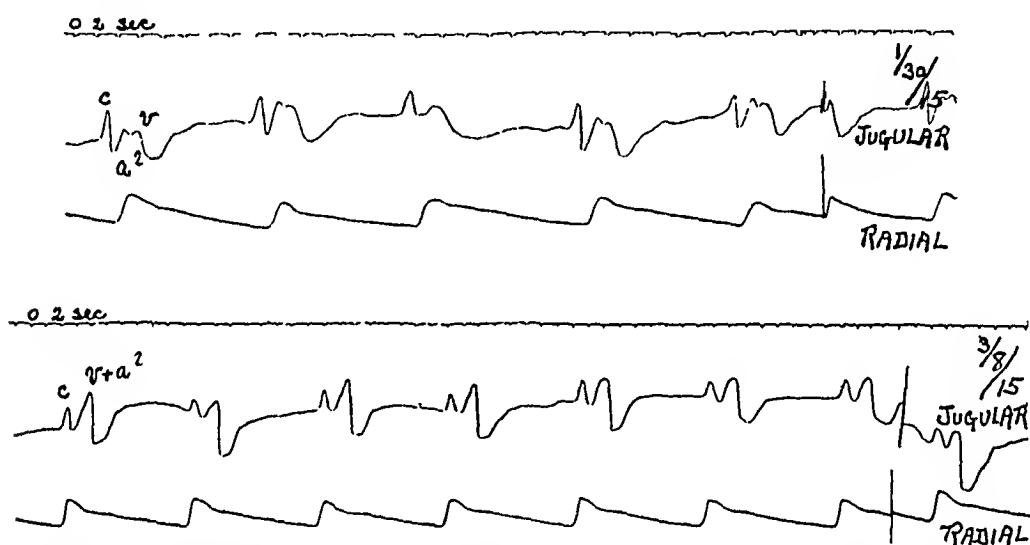


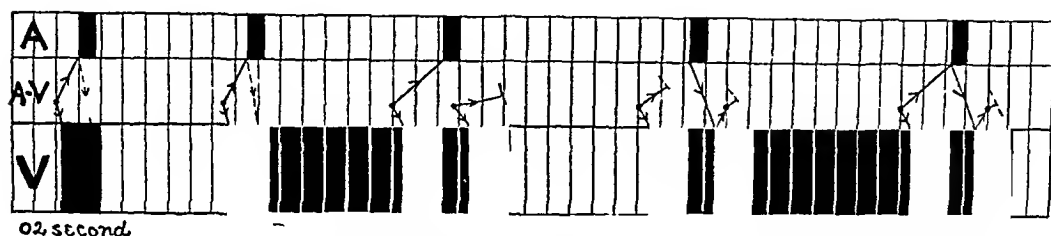
Fig 20—Polygrams showing jugular pulse above and radial pulse below. Taken January 30 and March 8, 1915. The auricular wave is apparently present preceding the *v* wave in the first record, and falling with the *v* wave in the second record.

that "the impulse center is not immediately on the path through which impulses pass from auricle to ventricle or ventricle to auricle, that it lies a little way off this channel and that a little time is lost while the impulse is traveling to it, though meanwhile the same impulse is passing on to stimulate the second main heart chamber." A diagram (Fig 21) has been constructed to illustrate the probable mechanism of the *a-v* rhythm in the patient recorded here, the three pairs of beats represent the three methods in the production of the coupling in the order given above. In the last instance the delay in the passage of the excitatory process to the auricle allows the ventricle time to recover from its refractory period so that it may respond to

⁹ Lewis, Th., and White, P. D. Heart 1914, 1, 359

the new stimulus. In support of the third explanation are the facts that the coupling comes only when the *R-P* interval is very long (about 0.300 second or over), that paired beats ensue whenever this extreme prolongation occurs, and that coupling fails to follow when a beat appears without any auricular complex during the period of long *R-P* intervals.

Dislocation of the *a-v* pacemaker downwards through the action of digitalis or of vagal pressure would account for but a small part of the prolongation of the *R-P* interval.



Feb. 21.—Diagram illustrating the *a-v* rhythm of W. S. The first two beats represent the average rate and time relations of his rhythm. The three pairs of beats illustrate the possible mechanisms in the production of the bigeminy. The first couple shows a premature beat arising in the *a-v* pacemaker with the auricle blocked off, the second couple shows the blocking off of the auricle in the first beat of the pair, and immediately following occurs a premature beat near the auriculo-nodal junction, the third couple shows the ventricle responding first to the excitatory process coming from the *a-v* pacemaker and shortly after to an impulse coming down from the auriculonodal junction, which impulse starts downward as soon as the junction has been reached by the slowly traveling excitatory process originating in the side-tracked *a-v* pacemaker (ordinarily there is no response to this stimulus because the ventricle is still in the refractory stage when the process reaches it, the dotted lines in the first two beats of the diagram represent the excitatory wave reaching the ventricle while it is refractory). Abscissae = 0.2 second.

SUMMARY

1 A cardiac rhythm is described which arises in the atrioventricular junctional tissues of a patient who showed flutter and fibrillation of the auricles prior to the onset of the present rhythm.

2 This atrioventricular rhythm responds in rate readily to exercise, forced respiration, vagal pressure, and atropin, but not to digitalis.

3 The sequence of contraction *vs-as* is lengthened by vagal pressure and by digitalis, the latter apparently acting more on the auriculo-nodal junction than on the pacemaker in the *a-v* tissues.

4 Atropin may shorten the *vs-as* interval prolonged by digitalis, but with the uninfluenced *a-v* rhythm the effect of atropin on the *vs-as* interval is overborne by the increase in the rate of the heart beat resulting from the action of the drug on the *a-v* pacemaker, under such circumstances the *R-P* interval is increased slightly.

5 Premature beats interrupt the rhythm rarely, on such occasions the returning cycles are not compensatory

6 Coupled 'beats of an unusual character appear when the *vs-as* interval is markedly prolonged by digitalis or by vagal pressure

7 The constancy of the atrioventricular rhythm and the failure of sino-auricular rhythm to be restored by atropin or by vagal pressure point to a loss of function of the sino-auricular node, its task as pacemaker being assumed by the atrioventricular junctional tissues

Thanks are due to Dr E W Taylor for permission to study this case, to Mr L S Brown and others who have been of assistance, and to the patient for his cooperation

THE CREATININ OF THE BLOOD IN NEPHRITIS ITS DIAGNOSTIC VALUE*

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The ability of the kidney to eliminate various substances administered either per os or parenterally has been practically employed by both the internist and surgeon as a means of determining its functional activity. The phenolsulphonephthalein test of Rowntree and Geraghty¹ and the lactose and potassium iodid tests of Schlayer and Takayasu² have found extensive use. More recently Neubauer³ has suggested the administration of creatinin as a functional test, since it is the one normal urinary constituent which is entirely endogenous and the rate of excretion of added creatinin may, therefore, be readily followed.

The functional condition of the kidney may be ascertained by two quite different modes of attack: by the amount of certain substances excreted by the kidneys, or by their retention in the blood. Since the introduction during the past two years of simple methods of blood analyses, especially at the hands of Folin and his co-workers, the latter method has received considerable attention. Simple but relatively accurate methods for the nonprotein and urea nitrogen, uric acid, creatinin and creatin have thrown light on many disputed questions of abnormal metabolism, and further, have disclosed new possibilities in the way of practical diagnostic tests. The retention of the various nitrogenous waste products in certain forms of nephritis has long been known, although it has been only recently that we have had adequate data on the distribution of these compounds.

Normally, the nonprotein nitrogen amounts to 25 to 30 mg, the urea nitrogen to 12 to 15 mg, the uric acid to 1 to 2 mg, and the creatinin to 1 to 2 mg, all calculated per 100 cc of blood. As an illustration of the extent of retention, we have encountered figures of 350 mg for the nonprotein nitrogen, 300 mg for the urea nitrogen, 27 mg for the uric acid and 33 mg for the creatinin⁴. Both the urea

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* From the Laboratory of Pathological Chemistry and the Medical Service of the New York Post-Graduate Medical School and Hospital

1 Rowntree, L G, and Geraghty, J T. Jour Pharm and Exper Therap, 1910, 1, 579

2 Schlayer and Takayasu. Deutsch Arch f klin Med, 1910-11, ci, 333

3 Neubauer, O. Munchen med Wchnschr, 1914, lxi, 857

4 Myers, V C, and Fine M S. Jour Biol Chem, 1915, xx, 391

and nonprotein nitrogen have been extensively employed for diagnostic purposes.⁵ In cases in which the nonprotein nitrogen and phenolsulphonephthalein tests have been simultaneously carried out, there has been a most excellent agreement between the two tests.⁶ There is this difference, however, the amount of the phenolsulphonephthalein excretion shows the renal function at the moment, whereas the nonprotein and urea nitrogen are rather a measure between the amount of waste nitrogen produced in metabolism and that eliminated by the kidney. In the early stages of nephritis, the phenolsulphonephthalein test probably yields the more valuable information, but after a decided retention has taken place, the nonprotein and urea nitrogen of the blood furnish a much more accurate index of the changes in the condition of the patient. With nonprotein nitrogen values over 60 mg and urea nitrogen values over 40 mg, the prognosis is bad. The dietetic treatment of nephritis based on the degree of nitrogen retention has likewise received favorable consideration.⁷

Ambard⁸ and other French workers have claimed that the relation between the concentration of urea in the blood and that eliminated in the urine furnishes a more reliable index of the functional condition of the kidneys than the content of the urea in the blood alone. Since the experiments of the French workers were conducted with unreliable methods, they have attracted comparatively little attention in this country. The very recent experiments of Marshall and Davis,⁹ and McLean and Selling¹⁰ with reliable methods appear, however, to support their contention.

As would seem probable, nephritis with retention is accompanied not only by an accumulation of urea in the body, but by the other nitrogenous waste products as well, especially uric acid and creatinin. This has been amply demonstrated by the observations of Folin and Denis, and Myers and Fine, who noted very high values for both uric

5 Folin, O, and Denis, W. *Jour Biol Chem*, 1913, xiv, 29, 1914, xvii, 487. Foster, N. B. *THE ARCHIVES INT MED*, 1912, x, 414, 1915, xv, 356. Agnew, J. H. *ibid*, 1914, xiii, 485. Frothingham, C, Jr, and Smilie, W. G. *ibid*, 1914, xiv, 541. Tileston, W, and Comfort, C. W, Jr. *ibid*, 1914, xix, 620. Farr, C. B, and Austin, J. H. *Jour Exper Med*, 1913, xviii, 228.

6 Frothingham, C, Jr, Fitz, R, Folin, O, and Denis, W. *THE ARCHIVES INT MED*, 1913, xii, 245. Frothingham and Smilie *ibid*, 1914, xiv, 541.

7 Folin, O, Denis, W, and Seymour, M. *The Nonprotein Nitrogenous Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism*, *THE ARCHIVES INT MED*, 1914, xiii, 224. Frothingham, C, Jr, and Smilie, W. G. *A Study of Different Nitrogenous Diets in Chronic Nephritis*, *ibid*, 1915, xv, 204.

8 Ambard, L. *Compt rend soc de biol*, 1908, lxxv, 712, 1910, lxxix, 411 and 506.

9 Marshall, E. K. Jr, and Davis, D. M. *Jour Biol Chem*, 1914, xviii, 53.

10 McLean, F. C, and Selling, L. *Jour Biol Chem*, 1914, xix, 31.

acid and creatinin in the severer cases of interstitial nephritis. Since atophan rapidly reduces the uric acid concentration of the blood in normal and gouty individuals,¹¹ but is without influence in the severer cases of nephritis with marked retention, Fine and Chace¹² have suggested its use as a means of determining the degree of renal involvement.

The marked retention of creatinin in the blood in uremia was noted independently and almost simultaneously by three different groups of investigators, Neubauer,¹³ Folin and Denis,¹⁴ and Myers and Fine.¹⁵ More detailed observations have since been presented by Myers and Fine¹⁶ while Foster¹⁷ has reported a few analyses of the total creatinin (creatinin plus creatin). It has long been known that in severe nephritis creatinin was generally excreted in decreased amounts,¹⁸ and it was quite logical to conclude from this that the permeability of the kidney to creatinin had been decreased. That such is the case is evident from the data at hand.

The present communication concerns itself primarily with the retention of creatinin in the blood, and since this occurs, practically speaking, only in nephritis, discussion will largely be confined to this condition. Although this retention of creatinin in uremia has been recognized now for more than a year, the subject has not received attention from a clinical point of view. In our hands the estimation of the blood creatinin has been of considerable prognostic value, cases showing over 5 mg per 100 c c of blood having invariably terminated fatally. Table 1 gives the results obtained in thirty cases of nephritis. To give a more comprehensive picture of the cases, the observations for the urea and uric acid of the blood, the blood pressure, the phenol-sulphonaphthalein output and the urinary findings have been included as well as the creatinin of the blood. The results of the blood analyses given in this table are those obtained at the height of the retention. The blood analyses of some of the older cases were reported in a previous paper,¹⁶ but are included here since the clinical side of the problem was not considered. For other and more detailed analyses on

11 Fine, M. S., and Chace, A. F. *Jour Pharm and Exper Therap*, 1914, vi, 219.

12 Fine and Chace. *THE ARCHIVES INT MED*. To be published.

13 Neubauer, O. *Munchen med Wchnschr*, 1914, lxi, 857.

14 Folin, O., and Denis, W. *Jour Biol Chem*, 1914, xvii, 487.

15 Myers, V. C., and Fine, M. S. *Proc Soc Exper Biol and Med*, 1914, xi, 132. Myers *Post-Graduate*, 1914, xix, 429.

16 Myers and Fine. *Jour Biol Chem*, 1915, xx, 391.

17 Foster, N. B. *THE ARCHIVES INT MED*, 1915, xv, 356.

18 Ditman, N. E., and Welker, W. H. *New York Med Jour*, 1909, lxxxix, 100, 1046, 1091 and 1134. Also Kraus, W. M. *THE ARCHIVES INT MED*, 1913, xi, 613.

these cases reference may be made to this paper Table 2 gives the figures for the creatinin, urea and uric acid of the blood at different intervals in seven of our recent cases of nephritis illustrating varying degrees of severity Figures for the creatinin of the blood in a large number of miscellaneous conditions are given in Table 3 with the view of showing that it is only in nephritis that high values for creatinin are encountered Figures for the creatin of the blood are not included in the present paper because they are not regarded as significant in this connection The question of the creatin of the blood will be discussed in another paper dealing with the urinary excretion of creatin

METHODS EMPLOYED

The phenolsulphonephthalein was administered intramuscularly according to the method of Rowntree and Geraghty¹⁹ and the excretion estimated with the Hellige colorimeter The methods which we have employed in the analysis of blood have already been described²⁰ It may be well, however, to outline the technic which has been used for the estimation of the creatinin

TECHNIC

In most of our work the Duboscq colorimeter has been utilized for the estimation of the creatinin and creatin somewhat after the technic described by Folin²¹ About 10 cc of blood are drawn directly from a vein into a small bottle containing a little powdered potassium oxalate or 5 drops of a 20 per cent solution to prevent clotting Six cc of the well mixed blood are treated with 24 cc of water (4 volumes) in a 50 cc centrifuge tube After the corpuscles have been laked, about 1 gram of dry picric acid is added, and the mixture stirred at intervals with a glass rod until it is a light yellow When the protein precipitation is complete, the tube is centrifuged and the supernatant fluid filtered through a small 7 cm filter paper From 17 to 21 cc of filtrate are usually obtained (5 cc of which are removed for the creatin estimation and 3 cc for the sugar estimation, if these determinations are to be carried out) To 10 cc of the filtrate is added 0.5 cc of 10 per cent sodium hydroxid, and a similar amount of alkali added to 10 cc of standard creatinin in saturated picric acid (containing 0.2, 0.5 or 1.0 mg creatinin to 100 cc of picric acid) Creatinin may now readily be prepared perfectly pure by the admirable method of Benedict²² A standard solution of this creatinin, 1 mg to 1 cc, is kept in 0.1 N hydrochloric acid From this we have prepared a stock solution in picric acid, 5 mg to 100 cc, by diluting 5 cc to 100 cc with saturated picric acid By pipetting 0.4, 1.0 and 2.0 cc of this solution into 10 cc graduates with a Mohr pipet and diluting to the mark, standards of the above strengths are prepared For the Duboscq colorimeter the standard prism can conveniently be set at the 15 mm mark

19 Rowntree, L. G., and Geraghty, J. T. *THE ARCHIVES INT. MED.*, 1912, ix, 284

20 Myers, V. C., and Fine, M. S., with the collaboration of Bailey, C. V., and Gorham, F. D. *Chemical Composition of the Blood in Health and Disease*, a series of papers reprinted from the *Post-Graduate* for 1914-15

21 Folin, O. *Jour. Biol. Chem.*, 1914, xvii, 457

22 Benedict, S. R. *Jour. Biol. Chem.* 1914, xxiii, 183

TABLE 1—CREATININ CONTENT OF THE BLOOD IN NEPHRITIS

Case	Age	Sex	Type of Nephritis	Result	Blood Analysis				Phtha lein, 2 Hour Out put	Blood Pressure		Urine		Remarks
					Creati nin, Mg to 100 cc	Urea N, Mg to 100 cc	Uric Acid, Mg to 100 cc			Sys tole	Dias tole	Albu min	Casts	
1 W F	25	♂	Mercury poisoning, uremia	Died	33.3	240	15.0			155	70	++	++	Uremic symptoms appeared one week previ ous to death although the creatinin had dropped to 14.8 mg. Died Dec 5, 1914
2 T D	34	♂	Chronic interstitial, uremia	Died	20.5	152	14.3		2.3	230	130	++	+++	Dizziness, retinal hemorrhages Died March 23, 1915
3 I D	17	♀	Chronic interstitial, uremia	Died	20.0	209	27.0		0	165	115	++	++	Marked pyorrhea alveolaris, moderate dilata tion of heart Died Jan 4, 1915
4 L C	50	♀	Chronic interstitial, uremia	Died	16.7	236	22.4		0	210	100	++	++	Died Jan 11, 1915, two days after admission
5 W O O	33	♂	Chronic interstitial, uremia	Died	16.6	182	11.4		1—	213		++	+	Slight edema of legs and ankles at time of admission, albuminuric retinitis, marked cyanosis and dyspnea Died May 10, 1914
6 M K	42	♂	Chronic diffuse, uremia	Died	14.7	170	11.0					++	++	Moderate hypertrophy of heart, marked ane mia and cyanosis, coma Both kidneys decapsulated on May 13, 1914 Patient died during operation
7 K K	39	♀	Chronic interstitial, uremia	Died	14.7	148	12.5		0.0	204	103	+++		Considerable cardiac hypertrophy, accentua tion of second aortic sound Died March 27, 1915
8 J W	34	♂	Chronic interstitial, uremia	Died	11.0	144	8.7		3.1	190	120	++	+	Occasional edema of ankles previous to admission, slight cardiac hypertrophy, marked neuroretinitis Died April 16, 1915
9 J S	50	♂	Chronic diffuse, uremia	Died	7.4	81	13.4			112	88	++	++	Slight edema of lower extremities, suppres sion of urine Died Nov 19, 1914
10 W G	8	♂	Chronic diffuse, edema, uremia	Died	7.0	94	5.5		3.8	153	105	+++	+++	Purpura hemorrhagica, marked general anasarca, died after being removed from hospital against advice
11 I T	30	♀	Chronic interstitial, edema, uremia	Died	5.3	100	15.4		10	225	160	++	+++	Wassermann +++++, generalized edema Died Jan 19, 1915
12 L P	57	♂	Chronic interstitial, uremia	Improved	4.8	80	8.0		1.31 10	225	145	++	+	Marked edema of feet and ankles previous to admission, thickening of arterial walls, left hospital improved
13 L R	52	♂	Chronic interstitial	Improved	4.6	40	5.5		47	167	98	++	++	Edema of ankles, marked accentuation of second aortic sound, left hospital Jan 24, 1915

14 L R	52	♀	Chronic Interstitial	Improved	3 3	17	4 1	16	180	94	+	+	+	Epigastric pain, vomiting, enlarged liver, paroxysmal tachycardia, slight edema of feet and ankles, left hospital Dec 12, 1911 Wassermann +++++, generalized edema, still in hospital
15 I P	71	♂	Chronic diffuse	Improved	3 2	72	8 3	25 15-43	235	130	++	++	++	
16 L B	64	♀	Chronic Interstitial	Improved	3 1	33	2 2	56	252	125	+	+	+	Slight edema of feet and ankles, slight cardiac hypertrophy, left hospital improved, Jan 24, 1915
17 L S	23	♀	Chronic parenchymatous	Improved	3 1	18	4 6	31 33	116	75	++	++	+	Slight edema of feet and ankles, enlarged tonsils, teeth in poor condition, left hospital improved
18 O M	55	♂	Chronic diffuse	Improved	2 9	16	3 6	29 43	210	125	++	++	++	Generalized edema and ascites, glycosuria and hyperglycemia (0.20 per cent), improving
19 I M	50	♂	Chronic interstitial	Improved	2 8	18	6 0	22	196	144	++	++	++	Arteriosclerosis, left hospital improved
20 H B	59	♀	Chronic Interstitial	Slightly improved	2 8	17	5 9	2 8 39	145	90	++	++	++	Patient does not appear ill despite the low phthalein output
21 F G	20	♀	Pyonephrosis	Unchanged	2 7	24		25	110	55	++	++		Left hospital against the advice of physician
22 F S	51	♀	Chronic Interstitial	Unchanged	2 6	14	2 9	42	150	80	+	+	++	Cholelithiasis, cholecystitis, patient still in hospital
23 A S	44	♀	Chronic interstitial	Improved	2 5	27		74	216	140	++	++	++	Patient appeared to show some uremic symptoms on admission
24 L S	55	♂	Chronic Interstitial	Unchanged	2 1	29	6 3		175	65	+	+	+	Wassermann +++++, spinal fluid +++++, aortic insufficiency, left hospital improved
25 W McL	42	♂	Chronic Interstitial	Improved	2 1	20	4 0	34	165	110	+	+	+	Epistaxis, headaches, anemia, left hospital improved
26 F B	60	♂	Chronic diffuse	Died	1 8	29	4 5	33	170	115	++	++	++	Marked dyspnea, fluid in abdomen Died on June 16, 1914
27 H S	37	♀	Chronic interstitial	Died	1 8	25	2 9	17 3-12	143		++	++	++	Generalized edema, double decapsulation Died March 27, 1914
28 F S	67	♂	Chronic Interstitial	Unchanged	1 5	10	4 2	22 10	114	77	+	+	+	Arteriosclerosis, cystitis
29 H K	26	♂	Acute parenchymatous, edema	Improved	0 9	15	2 6	29 32	125	72	++	++	++	Double decapsulation
30 A K	52	♀	Chronic interstitial	Improved	0 9	28	3 6	39	182	105	+	+	+	Physical examination negative

TABLE 2—PROGRESSIVE CHANGES IN THE CREATININ, UREA AND URIC ACID OF THE BLOOD IN TYPICAL CASES OF NEPHRITIS

Case	Date	Blood Analyses			Remarks
		Creat- inin, Mg to 100 c c	Urea N, Mg to 100 c c	Uric Acid, Mg to 100 c c	
7 K K	3/20/15	9.4	110	10.9	Patients showed definite uremic symptoms on admission and rapidly went into coma and died
	3/24/15	9.7	138	12.4	
	3/26/15	14.7	148	12.5	
4 E O	4/ 9/15	11.5	90	15.9	
	4/11/15	16.7	236	22.4	
2 T D	1/22/15	7.8	60	7.0	
	1/27/15	10.0	67	7.0	
	1/30/15	8.9	77	6.8	
	2/ 6/15	8.4	72	6.0	
	3/ 9/15	11.0	97	9.1	
	3/16/15	11.4	120	10.8	
	3/19/15	14.1	131	10.5	
	3/23/15	20.5	152	14.3	
	3/23/15	20.5	152	14.3	
8 J W	2/24/15	8.3	55	8.1	Patients on admission in fair condition clinically and the approach of uremia did not appear evident. Both cases showed slight improvement on treatment, although Case 2 was evidently more severe than Case 8. With T. D. uremic symptoms appeared about two weeks before death, whereas with J. W. they were not evident until four days previous to death.
	3/ 1/15	6.5	63	5.6	
	3/ 6/15	5.3	89	6.0	
	3/19/15	6.5	51	4.2	
	3/25/15	6.1	51	7.0	
	4/ 8/15	8.0	61	7.2	
12 L P	4/15/15	11.0	144	8.7	Case 12 showed severe uremic symptoms on admission, but readily responded to treatment and left the hospital improved.
	1/ 6/15	4.8	180	8.0	
	1/22/15	3.6	65	2.2	
	2/18/15	3.1	59	3.6	
	3/ 1/15	2.9	37	4.9	
15 J P	3/ 5/15	2.5	45	2.5	Patient on admission showed some dyspnea and general anasarca, but readily responded to treatment.
	4/23/15	3.2	72	8.3	
	5/ 4/15	2.4	37	6.7	
18 O M	5/12/15	2.3	28	5.7	Patient entered hospital with great respiratory distress due to marked ascites. After abdominal paracentesis, symptoms were greatly relieved and the condition much improved. Blood sugar of 0.20 per cent.
	4/15/15	2.3	15	5.4	
	4/27/15	2.9	16	3.6	

TABLE 3—CREATININ CONTENT OF THE BLOOD IN MISCELLANEOUS CONDITIONS

Case	Clinical Diagnosis	Creatinin of Blood, Mg to 100 c c	Case	Clinical Diagnosis	Creatinin of Blood, Mg to 100 c c
31 C	Normal	13	64 H H	Acromegaly	10
32 H R		08	65 S	Amputation diabetic gangrene(?)	18
33 B		13	66 A F	Diabetes	15 (2)
34 S		16	67 M G		14
35 J F		09	68 P F		17
36 O O		12	69 J E		15
37 J B	Malnutrition	19	70 M Mc		11-38 Av 23 (6)
38 E B.		13	71 O L		09
39 I S		13	72 F R		1421 Av 17 (2)
40 S		15	73 R J		1930 Av 25 (2)
41 M F		19	74 M W		20
42 M S	Chronic interstitial nephritis	29	75 M Mc		1526 Av 20 (2)
43 F S		28	76 M W	Diabetes (blood did not show hyperglycemia)	22
44 A A		1024 Av 17 (2)	77 A B		26
45 Dr M		22	78 O N		23
46 R O		11	79 J G		10
47 F S		26	80 B		13
48 S R	Acute parenchymatous nephritis	12	81 L J	Gout	22
48 E G	Nephroptosis	28	82 P O'N		0815 Av 11 (4)
50 F	Endocarditis	31	83 T B		0922 Av 14 (8)
51 H S	Carcinoma of bladder	18	84 J L		17
52 J L	Carcinoma	14	85 W L		25
53 S	Brain tumor	20	86 J H		08
54 J K	Hyperthyroidism	31	87 M B	Arthritis	1122 Av 15 (3)
55 B S	Exophthalmic goiter	22	88 M L		1525 Av 20 (2)
56 J E	Leukemia	1828 Av 22 (2)	89 J S		21
57 T v S	Pernicious anemia	1423 Av 18 (2)	90 Dr S		22
58 M S	Secondary anemia	08	91 M A		1422 Av 18 (2)
59 H B	Secondary anemia with hemorrhoids	12	92 A O		26
60 J B	Hemolytic jaundice	22	93 A K	Acute articular rheumatism	21
61 B W	Bronchial asthma	23	94 A G	Pleurisy with effusion	22
62 T	Neurasthenia	16	95 J M	Gumma of liver	10
63 L	Cholelithiasis	21	96 L M	Carcinoma of liver	11

NOTES ON CASES WITH HIGH CREATININ VALUES

- 42 Phthalein 35 per cent., many casts, but no albumin
- 43 Phthalein 30 per cent., trace of albumin
- 47 Phthalein 39 per cent.; moderate amount of albumin and moderate number of casts
- 49 Phthalein 75 per cent., few casts, but no albumin
- 50 Phthalein 52 per cent., Wassermann, one plus, moderate amount of albumin and many red blood cells; systolic blood pressure 165
- 54 Heart block, 0.5 per cent. sugar in urine
- 70 Phthalein 52 per cent., trace of albumin
- 73 Phthalein 36 per cent., moderate amount of albumin
- 75 Phthalein 71 per cent., moderate amount of albumin and moderate number of casts
- 77 Gastric ulcer, trace of albumin
- 92 Phthalein 58 per cent., moderate amount of albumin, few casts

The estimation of the creatinin may likewise be carried out with the use of the Autenrieth-Konigsberger colorimeter of Hellge. In this case less blood is necessary. Two c.c. are treated in a cylindrical centrifuge tube with 8 c.c. of water and other manipulations as above. For the determination proper, 0.1 c.c. of 10 per cent sodium hydroxid are added to 2 c.c. of the picric acid filtrate in a small test tube. Simultaneously 1 c.c. of the alkali is added to 20 c.c. of a saturated solution of picric acid containing 15 mg creatinin to 100 c.c. to serve as standard for the wedge. At the end of ten minutes the wedge is filled with the standard, the cup with the unknown, and readings made. Although it is well to calibrate a wedge for a given instrument, the following formula, in which R represents the colorimetric reading and 5 the dilution, will suffice:

$$89 - R \times 0.0179 \times 5 = \text{mg creatinin calculated per 100 c.c. of blood}$$

DISCUSSION

Of the eleven cases in our series²³ (Table 1) showing over 5 mg of creatinin per 100 c.c. of blood, all terminated fatally in from a few days to two months. In this group of cases the phthalein output was practically zero, with the exception of Case 11, and here the test was carried out over two months before death. It should perhaps be noted that Case 20 on the first two tests showed very low phthalein outputs, although the creatinin of the blood was only slightly raised. Cases 12 and 15 with very high figures for urea nitrogen (80 and 72 mg) and uric acid (80 and 83 mg), but with comparatively low values for creatinin (48 and 32 mg), showed considerable improvement under treatment.

From the distribution of the nonprotein nitrogenous compounds in the blood and urine, it would appear that of the three constituents mentioned, creatinin was normally the most readily, and uric acid the least readily, eliminated, with urea standing in an intermediate position (see Table 4). From this it is logical to expect that the excretion of uric acid would be the first to be impaired. In gout this is apparently the only constituent for which the permeability is lowered, while in nephritis our blood studies appear to indicate that a retention of uric acid is generally the first to become evident. In harmony with this hypothesis we should next expect a retention of urea, and lastly that of creatinin. This appears to correspond fairly well with the facts in most cases. It seems reasonable to conclude that when a noticeable retention of creatinin has occurred, the functional condition of the kidney has been gravely impaired. In our experience creatinin values from 2.5 to 3.0 mg per 100 c.c. of blood should be viewed with suspicion and figures of from 3.0 to 5.0 mg regarded as decidedly unfavorable, while figures over 5 mg probably indicate an early fatal termination.

²³ For the opportunity of studying these cases we are under obligation to the Director of the Medical Department, Dr Edward Quintard. We are also indebted to Drs A. F. Chace and R. A. Cooke and other members of the medical staff for many courtesies extended to us, and to Dr M. S. Fine of the Laboratory of Pathological Chemistry for the uric acid estimations he has collected on this series of cases.

Theoretically the amount of the increase in the creatinin of the blood should be a safer index of the decrease in the permeability of the kidney than either urea or uric acid, for the reason that creatinin on a meat-free diet is entirely endogenous in origin and its formation (and elimination normally) very constant. Urea, on the other hand, is largely exogenous under normal conditions and its formation, therefore, subject to great fluctuations, the same being true in a measure of uric acid.

Of the data given in Table 2, the creatinin figures indicate especially well the condition of the patients at the time the examinations were made. The values found for the creatinin in Case 12 dropped gradually with the improvement in the case, but an inspection of the table does not show the same regularity in the decline of the urea and uric acid. The same remarks might be made in a general way for Cases 2 and 8. With the improvement there was a decline in the creatinin, while with the relapse the values soon passed their former maximum and gradually rose until the fatal termination. As would seem evident from this table, the blood analyses are much more valuable than the phthalein in showing slight changes in severe cases of nephritis.

TABLE 4—COMPARATIVE NITROGEN PARTITION OF URINE AND BLOOD IN PER CENT OF TOTAL NONPROTEIN NITROGEN

Fluid	Urea N	Uric Acid N	Creatinin N	Ammonia N	Undetermined N
Normal urine	85	2	5	4	4
Normal blood	50	2	2	0.3	46
Blood in severe uremia	75	2.4	2.5	0.5	20
Blood in chronic nephritis	55	2.2	2	0.3	41
Blood in gout	50	6.0	2	0.3	42

We have taken occasion to estimate the creatinin content of blood in a large number of miscellaneous conditions, the results of which are given in Table 3. In eleven of these cases figures between 2.6 and 3.1 were found. Three of these had been diagnosed as nephritis but this was not true of the remaining eight. An inspection of the histories of these cases (diabetes, arthritis, carcinoma, endocarditis), however, showed almost invariably evidence of some renal involvement. It is of interest that in gout with its uric acid retention there appears to be no appreciable retention of creatinin. It seems safe to conclude that the creatinin of the blood is raised only in conditions resulting in a decreased activity on the part of the kidney.

There seems to be no evidence, as already pointed out,¹⁶ which definitely supports the view that the retention of metabolic end products such as urea, uric acid and creatinin, are themselves the cause of uremic symptoms. In Case 1, of mercury poisoning, uremic symptoms did not appear until a week after maximum concentrations had been attained. The possibility that a decomposition product of creatinin¹⁸ such as methylguanidine, might play a part in the development of uremia, should perhaps still be considered, although we now possess other explanations for the onset of this condition.²⁴

CONCLUSIONS

The estimation of the creatinin of the blood in nephritis is a very simple but valuable diagnostic and prognostic test. The creatinin rises above 2.5 mg per 100 c.c. of blood almost without exception only in conditions with renal involvement. Creatinin values from 2.5 to 3.0 mg may be viewed with suspicion, figures from 3.0 to 5.0 mg regarded as decidedly unfavorable, while over 5.0 mg probably indicate an early fatal termination.

24 Peabody, F. W. *THE ARCHIVES INT. MED.*, 1914, xiv, 236

A METHOD FOR THE DETERMINATION OF PLASMA AND BLOOD VOLUME *

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AND

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BALTIMORE

Routine red cell counts and hemoglobin determinations yield information that is valuable but very incomplete. This information concerns only the concentration of the blood. These routine methods do not furnish us absolute values for hemoglobin, for red cells, or for the oxygen-carrying capacity of the blood. With them, an anemia may be more apparent than real, as it may be dependent on or associated with a marked increase in plasma volume, while a polycythemia does not necessarily indicate an absolute increase in red cells, as it may be dependent on a decrease in plasma. In order to obtain absolute values for either red cells or hemoglobin, data relative to plasma volume or total blood volume are essential.

The volume as well as the concentration of the blood must play a rôle in pathological physiology. Absolute values are essential to the proper interpretation of certain pathological findings. Is an increase in the blood mass with overfilling of the vascular system in any way responsible for hypertension? Is the large heart frequently seen in pernicious anemia due to a large blood volume? Is the large heart sometimes seen in myocardial insufficiency (unassociated with hypertension or nephritis) due to an increase in blood mass? Questions such as these must remain unanswered until data concerning absolute values are correlated with pathological findings.

With so great variations in size and weight of individuals, the normal values for plasma and blood are best expressed in percentages or fractions of the body weight, or as the number of cubic centimeters per kilogram of body weight. Since the work of Welcker, the blood has been considered to constitute one-thirteenth of the body weight. Recently, the values obtained by Haldane and Smith (one-twenty-first), and by Plesch (one-nineteenth) have been frequently accepted. The methods affording these last values are not without serious drawbacks from the points of view of inherent technical error, complicated nature of apparatus required and the possibility of injury or discomfort attending their use.

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* From the Medical and James Buchanan Brady Urological Clinics of the Johns Hopkins Hospital

There is a distinct need for a simple method for the determination of plasma and blood volume, particularly for a method that can be repeatedly applied without injury to the patient

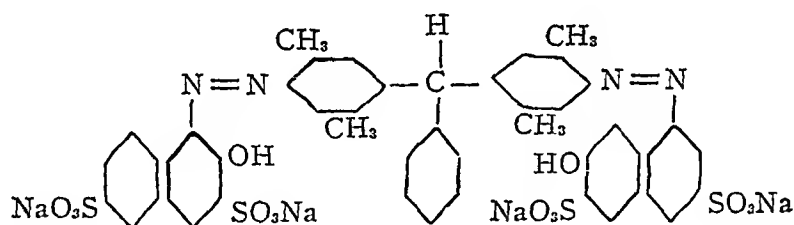
THE PRINCIPLE OF THE METHOD

The principle underlying this method is the introduction directly into the circulation of a non-toxic, slowly absorbable dye, which remains in the plasma long enough for thorough mixing, and the determination of its concentration in the plasma colorimetrically by comparison with a suitable standard mixture of dye and serum

A dye which would fulfil these conditions was sought. Certain of the phthaleins were tried and discarded because of the rapidity with which they leave the vascular system. Dr Herbert M. Evans, of the Anatomical Department, when consulted in regard to dyes remaining for a long time in the circulation, suggested the possibilities of vital red, and supplied us with the dye used in this work. It is with great pleasure that we acknowledge our indebtedness to him.

SOME PROPERTIES OF THE DYE

Vital red is disodium disulphonaphthol azotetramethyl triphenyl methane



It is water soluble to the extent of $1\frac{1}{2}$ per cent. In dilute solutions of 0.01 per cent, it does not dialyze against water through collodion sacs even in forty-eight hours. Under such conditions, the dye is practically adsorbed by the dialyzing membrane.

When its toxicity was determined by intravenous injection into animals, it was found that doses exceeding from 5 to 10 mg per kilo sometimes resulted in a slight transient albuminuria. Smaller doses were harmless, so far as could be ascertained. Three mg per kilo was chosen as the most suitable amount for our purposes. Protocols of cats and dogs studied for toxicity appear below.

TOXICITY EXPERIMENTS

PROTOCOLS

CAT 1—Weight, 24 kg, given 750 mg intravenously, killed in three hours.

CAT 2—Weight, 275 kg, given 700 mg intravenously, killed in twenty hours.

CAT 3—Weight, 175 kg, given 6 mg to kilogram intravenously, no effect, urine free from albumin afterward.

Dog 5—Weight, 7 kg Nov 4, 1914 Given 600 mg, vitally stained, no toxic manifestations One week later, 40 per cent of dye still in circulation

Dec 17, 1914 Blood still contains considerable dye

March 1, 1915 Animal still slightly vitally stained after a period of four months On only one occasion during this whole period was a trace of albumin found in the urine.

Dog 8—Weight, 6.85 kg Nov 17, 1914 Given 350 mg

Nov 18, 1914 Considerable albumin in urine, no casts, some red blood cells

Nov 22, 1914 Advanced distemper Urine free from albumin

Nov 26, 1914 Died with distemper

Dog 9—Weight, 9.9 kg Nov 21, 1914 Given 99 mg Dog was normal except for a faint trace of albumin found in the urine on first and second days

Dog 10—Weight, 5.5 kg Nov 21, 1914 Given 55 mg, normal, no albumin

In order to vitally stain the tissues even slightly, it was found necessary to use at least 10 mg per kilo If a strong solution is injected locally into the subcutaneous tissues, the tissues are stained a beautiful bright red color, which persists unaltered for many months This accident happened with patients on two or three occasions early in this work, but since has been avoided by ascertaining with certainty that the needle was in the lumen of the vein before the dye was injected

Traces of the dye appear in the urine and in the lymph flowing from the thoracic duct at the end of ten minutes The dye continues to be excreted in the urine of patients for from three to four days following a dose of 3 mg per kg Following this amount no evidence of the dye in the tissue cells or white blood cells could be found with the oil immersion The fate of all the dye has not been determined, but considerable amounts can be found in the plasma for three or four days following its injection

TECHNIC

A 1.5 per cent solution of the dye in freshly distilled water is prepared and sterilized by boiling for from five to ten minutes, and aseptically stoppered in a sterile Erlenmeyer flask This solution is made up as required

The patient is weighed (stripped) and the dose determined on a 3 mg per kilo basis The skin over the anterior surface of both elbows is cleaned up in the usual manner for venepuncture Under aseptic technic, a small platinum-iridium needle (20 gauge) to which is attached a short piece of rubber tubing (from 2 to 3 cm in length) is inserted into the vein Ten c.c. of blood are withdrawn into a pipet and emptied into a 50 c.c. centrifuge tube containing just sufficient powdered sodium oxalate to prevent coagulation The plasma so obtained is used in the preparation of the standard which is described

later¹ The rubber tubing is removed from the needle, the latter being left in the vein and a 20 c c Record syringe containing the exact dose² of the dye is attached, and its contents injected, after which the needle is withdrawn Three minutes later, a needle is inserted into the vein of the opposite arm Without impeding the venous return, 10 c c of blood are withdrawn immediately by means of a pipet, two or three minutes later, 10 c c more are withdrawn The first is placed in a 50 c c centrifuge tube, the second in a 15 c c graduated centrifuge tube To each, sufficient dry oxalate is added to prevent clotting, and the tubes are capped with rubber to prevent evaporation during centrifugalization

The three tubes are placed in a high-power centrifuge and subjected to 3,000 revolutions per minute for twenty minutes³ After removal from the centrifuge, the relative proportions of erythrocytes and plasma in the graduated tube are noted Without disturbing the red cells, the plasma is carefully pipetted off from each tube and placed in a clean test tube We now have three test tubes, (1) containing plasma without dye, (2 and 3) containing plasma with dye in an unknown concentration A suitable dye-plasma standard mixture of known dye content must be prepared, and with it 2 and 3 are compared

The standard dye preparation⁴ is made as follows 0.5 c c of the dye solution used for the injection is brought up accurately to 100 c c

1 This procedure of taking plasma for mixing the standard in each case was found necessary on account of the great variation in the color of the plasma in different individuals

2 The amount injected is 3 mg per kg The weight in pounds divided by eleven gives the number of cubic centimeters of a 1.5 per cent solution to be injected

3 To prevent hemolysis, all pipets and centrifuge tubes must be thoroughly washed with normal saline solution and dried before use It is obvious that the slightest hemolysis will alter the color of the plasma and make accurate colorimetric readings impossible

4 Obviously the standard must be sufficiently intense in color to insure the patient's readings falling on the scale Since the smaller the amount of plasma in relation to the body weight the greater will be the intensity of the dye, a standard must be chosen which will be more intense than the plasma-dye mixture obtained from normal patients having the smallest proportion of plasma in relation to body weight The standard selected has been prepared on the following basis The amount of drug injected is placed in the number of cubic centimeters of salt solution corresponding to the number of grams represented by 4 per cent, of the body weight, or, expressed differently, in the amount of salt solution represented by 40 c c for every kilogram of body weight, this amounts to 5 c c (75 mg of dye) of the solution injected, to 100 c c of 0.8 per cent sodium chlorid For example, a man weighing 70 kilos would be given 210 mg of dye (3 mg per kg), which is equal to 14 c c of a 1.5 per cent solution Four per cent of 70 kg is equal to 28 kg, and without making a correction for the difference in specific between the blood plasma and water, this would amount to, roughly, 2,800 c c If 210 mg are dissolved in 2,800 c c, then 75 mg should be dissolved in 100 c c

with 0.8 per cent saline. One part of this is mixed with one part of the patient's plasma and two parts of salt solution, yielding a dilution of 1 in 4. With this solution, the prism of the colorimeter (Rowntree and Geraghty's modification of the Autenrieth-Konigsberger apparatus) is filled. This dilution has been found to be well adapted to colorimetric determinations. Each of the specimens (2 and 3 of the patient's plasma) is diluted with three parts saline and placed in the cup of the colorimeter and read against the above standard.

CALCULATION OF RESULTS

The method described above furnishes volume values for plasma and total blood. When it is desired to express values as per cent of body weight, the formulas given below can be utilized. Since the specific gravities of the plasma and of the blood were not ascertained in this study, one of 1.050 for the whole blood and of 1.030 for the plasma have been used.

FORMULAS

Plasma Volume—Weight of patient in kg = W

Standard prepared so that amount of dye injected is diluted in 40 cc for every kg of body weight

Reading of standard prepared as directed = 100

Reading of patient's plasma against standard = R

The number of cc of plasma in patient's body = $100/R \times 40 W = 4,000 W/R$

Percentage of Body Weight—Plasma volume in cc \times Sp G of plasma/1,000 = weight of plasma = X

$X \times 100/W$ = per cent of body weight

Cubic centimeters of plasma per kg = No cc in body/W

Total Blood Volume—Let hematocrit reading of the volume occupied by corpuscles = P

Volume of plasma = $100 - P$

Total blood volume = plasma volume $\times 100/100 - P$

Total Blood as Per Cent of Body Weight—Total blood volume in cc \times Sp G/1,000 = weight of total blood = Y

$Y \times 100/W$ = per cent of body weight

Cubic centimeters per kg = number cc in body/W

UNDESIRABLE FEATURES OF THE METHOD

Hemolysis—Sometimes the colors do not match perfectly in quality. This is the result of hemolysis and of necessity makes the quantitative determination more difficult. It is extremely infrequent, however, to find this failure with both specimens, and on the one or two occasions when this has occurred, the determination was not attempted. Records have been kept throughout as to the matching of the colors. In a large proportion of instances the colors in both specimens were perfect. Where the matching was only slightly imperfect, readings were made and in many instances these have closely approximated readings of the other specimen in which the color was perfect. In

spite of the most careful technic, inexplicable hemolysis occurred at times. It is considerably more frequent in the narrow graduated centrifuge tube used for the hematocrit values.

Lipemia—Lipemia, if very marked, makes the determination impossible. Only once has this been encountered. In a few instances it offered some slight difficulty. By proper attention to diet and to the time of making the determination, this difficulty can be readily obviated. In our series it has not been sufficiently troublesome to require such measures.

Discomfort to Patient—Aside from the slight pain of the venepuncture, the patient usually suffers no discomfort or inconvenience. In approximately 9 per cent of the cases, chilly sensations occurred, while in five instances, chills, with fever reaching to 101, were seen. None of the normal cases exhibited thermic responses. They are apparently more common in cases of anemia.

CONTROLS OF THE METHOD

Controls on the method have been made in order to determine the constancy of its findings under various conditions and in order to justify certain steps in the technic. These studies are here presented under subheadings. Controls on the plasma method are first considered and later those on the hematocrit method of determining total blood volume.

A Rate of Disappearance of Dye from Blood—Throughout the work, readings have been made at three minute and six minute intervals. The following afford striking proof of the slowness with which the dye disappears from the circulation. In a series of thirty-six cases in which the color matching was equally good in both determinations, nine cases showed identical reading for the two determinations, nine showed higher readings for the second, the average amount above the first being 2.5 per cent, while eighteen showed higher readings for the first determination, the average amount above the second being 3 per cent. This indicates that some dye does disappear from the circulation during the time of determination, but also indicates that the loss is inconstant and small. On rare occasions, marked discrepancies in the two readings occur. Such determinations should be discarded.

Below is shown the rate of disappearance of the dye from plasma in a man over a period of twelve minutes, readings being made at approximately two-minute intervals, and the amount of dye of the first determination being considered 100 per cent.

J C, weight 55.4 kg, 178 mg dye injected

Time Elapsing Minutes ⁵	Per Cent
2	100
4	104
6	103
8	102
10	102
12	97

Rate of Disappearance of Dye from the Circulation in Dogs—Protocols 1 and 2 indicate the slow rate of disappearance of dye from the blood of dogs the amount present on first determination being considered as 100 per cent.

Dog 1—Weight, 77 kg, 23 mg dye injected

Time Elapsing Hours, Minutes	Per Cent
13	94
30	92
2 20	65
3	60
6	52
24	26

Dog 2—Weight, 95 kg, 100 mg dye injected

Time Elapsing Hours, Minutes	Per Cent
2	93
4	93
10	86
12	86
15	81
1 6	77
1 8	73

These data demonstrate that the absorption from the blood stream is slow, and justify us in accepting determinations made within six minutes of the time of injection of the dye. Further proof of the slowness of the absorption is shown by the fact that on several occasions the plasma three to four days after injection showed a considerable amount of the dye. The urine also shows traces for some days after the injection.

B Values Found on Repeated Determinations—Repeated determinations on the same individual yield practically identical results, provided no appreciable change in the patient's condition has occurred. Some of these persons are normal and others are suffering from chronic disease in which no appreciable change occurred during the interim.

⁵ The first reading at two minutes was lower than subsequent ones. Mixing was probably not complete in two minutes.

TABLE 1—REPEATED DETERMINATIONS ON MEN

Name	Date	Weight	Volume in c c	Cubic centi- meters per Kg
OI	2/ 2/15	58	2,922	50
	2/ 4/15	58	3,030	52
FI	2/ 2/15	67	2,969	44
	2/ 4/15	67	3,037	45
D	3/11/15	57	2,665	47
	3/12/15	57	2,681	47
G	3/11/15	64	3,176	50
	3/12/15	64	3,083	48
B	1/ 7/15	61	3,036	49
	2/ 6/15	64	3,165	49
T	2/12/15	50	1,975	40
	2/25/15	50	1,990	40
Fr	1/20/15	62	3,056	49
	3/18/15	63	3,160	50
I	1/12/15	81	3,172	39
	2/ 3/15	80	3,064	38
W	4/22/15	64	3,375	53
	5/ 3/15	65	3,400	53

Dogs do not give so constant results but it is altogether probable that the dogs' plasma volume is subject to relatively greater and more sudden changes than that of man. Some interesting findings on dogs are included in Table 2.

TABLE 2—REPEATED DETERMINATIONS ON DOGS

No	Date	Weight	Plasma, c c	O c per Kg	Remarks
1	1/19	10.5	696	66.3	
	1/27	9.35	623	66.6	Distemper
	2/ 1	8.1	572	70.6	
	2/ 3	7.65	481	62.8	Following immediately a bleeding of 165 c c
	2/ 4	7.62	651	85.5	Next day
			958	126	After infusion of 325 c c
2	1/27	9.05	603	66	
	2/15	9.02	635	61	
4	1/19	15	1,202	81.1	Distemper — bled 300 c c six minutes before first sample
	1/21	15	1,137	76.4	

C Plasma Volume Determined with Varying Amounts of Dye—
The same value for blood volume is obtained whether one works with 2, 3 or 4 mg per kilogram. Three practically normal men were studied.

in this connection Determinations made after injection of 2 and 3 mg doses yielded values within 75 cc in two instances, while in the third, 2 and 4 mg per kilogram were used, the results agreeing within 1 per cent Three mg per kg is considered absolutely satisfactory, yielding colors well adapted to colorimetric determination

D Controls on the Colorimeter—In the past, in making parallel series of readings with various phthaleins and with Folin's micro-Kjeldahl method, practically identical readings were obtained with two instruments, the Duboscq and our colorimeter In a small series of parallel readings made in this investigation, identical readings were also obtained with both

E The Loss of Blood at Venesection Demonstrated—The method was applied to three men before and after phlebotomy The results appear in Table 3 Nos 1 and 2 were normal donors for transfusion and No 3 was a hypertensive patient, the subject of a therapeutic venesection⁶

TABLE 3—LOSS OF BLOOD AT VENESECTION

Name	Volume Before	Amt Bled	Volume After
1 G	Plasma, 3,180	300	Plasma, 2,862
2 D	Plasma, 2,790	620	Plasma, 2,573
	Blood, 5,083		Blood, 4,274
3 A	Plasma, 3,872	800	Plasma, 3,425
	Blood, 6,143		Blood, 5,434

A decrease corresponding fairly well to the amount of blood removed is demonstrated in all three cases

F Hematocrit—The whole blood volume is calculated from the plasma volume on the basis of the hematocrit findings, after centrifugalization in graduated tubes for 3,000 revolutions per minute for twenty minutes A longer period was unnecessary, the packing always reaching its maximum within this time The values from the same individual varied but little, whether the samples were obtained with free circulation of blood or after impeding the venous return for as long as fifteen minutes When the venous return was cut off, the red cells increased 4 per cent and 5 per cent in two instances and decreased 2 per cent and 5 per cent in two others Where possible, it is better to take sample for hematocrit determination from the freely

⁶ The Lindeman method of transfusion was used and the amount of blood measured

circulating blood Repeated determinations on the same normal individual give close but not identical values Undoubtedly some opportunity for error is here afforded

G Is the Dye Taken Up by the Red Blood Cells?—Early in the course of this work it became evident that the dye was not readily taken up by tissue cells or the cells in the blood stream From the experiments with collodion sacs previously mentioned and from the fact that neither the erythrocytes nor leukocytes were stained when observed in fresh blood preparations, it seemed fair to surmise that most of the dye remained in the plasma during the short time of the determination In order to get at this question quantitatively, it was first necessary to determine the relative amounts of plasma and red blood corpuscles in the whole blood Several methods have been employed for this purpose, among others, the various forms of the hematocrit and the nitrogen method devised by Bleibtreu⁷ The hematocrit method described above was found to be the most satisfactory for our purpose, yielding figures that agreed closely with those obtained by other workers with this method In two different samples of blood, the relative amounts of plasma and erythrocytes were determined by the hematocrit and by the nitrogen method The latter gave a plasma value 4 per cent to 9 per cent higher than that of the hematocrit Bleibtreu's figures were also high compared with those of other observers using the hematocrit method In our work, the hematocrit values only were taken

In order to determine whether the dye is absorbed by the blood cells, and, if so, to what extent, the following procedure was adopted Fifty cc of blood were taken from a healthy man and rendered incoagulable with powdered sodium oxalate Ten cc of this blood were used for hematocrit determination, 15 cc being centrifuged and the plasma pipetted off The remainder was agitated until measured out for the experiments given below

Experiment 1—Centrifuge Tube 1 Fifteen cc of this whole blood plus 2 cc of dye solution plus 13 cc of saline

Centrifuge Tube 2—Five cc of plasma plus 1 cc of dye solution plus 4 cc of saline

After Tube 1 was centrifugalized,⁸ the plasma was pipetted off and compared with the plasma dye mixture from Tube 2, which was placed as the standard in prism of the colorimeter The reading was 80 Therefore, in dilutions used, Tube 1 contained 80 per cent as much dye per cubic centimeter as Tube 2 The relative amount of plasma in the blood in Tube 1, as shown by the hematocrit, is 62.5 per cent

Then $15 \times 62.5 = 937$ cc plasma in Tube 1

⁷ Bleibtreu, M and L Eine Methode zur Bestimmung des Volums der körperlichen Elemente im Blut, Arch f Physiol (Pflüger's), 1892, li, 151

⁸ Three thousand revolutions per minute for twenty minutes

Then 2 cc of dye solution is diluted in 24.37 cc, or 1 cc in 12.18 cc

Or there should be 10/12.18, 82.9 per cent of dye in Tube 1

Colorimeter reading, as calculated from hematocrit data, 82.9 per cent

Colorimeter reading observed, 80 per cent

Experiment 2—Experiment 1 was repeated with the blood taken from another normal individual

Colorimeter reading, as calculated from hematocrit data, 81.8 per cent

Colorimeter reading observed, 82 per cent

Experiment 3—Experiment 1 was repeated with the blood taken from a third normal individual

Colorimeter reading, as calculated from hematocrit data, 81.4 per cent

Colorimeter reading observed, 81 per cent

In considering the foregoing experimental data, several factors should be noted. The hematocrit must necessarily give us the minimum value for the amount of plasma in the blood, as the corpuscles are wet and the interstices are filled with fluid. Therefore, the hematocrit findings for plasma must be slightly low, and the calculated colorimeter reading slightly high. If the dye is absorbed by or diffuses into the corpuscles, the observed colorimeter readings will be low, that is, the plasma volume large. As the calculated and observed figures agree so closely, the amount of dye lost from the plasma must be negligible. From the foregoing experiments, it would seem safe to conclude that *in vitro* little or none of the dye passes into the blood cells.

RELATION OF BLOOD AND PLASMA VOLUME TO BLOOD PRESSURE

At the suggestion of Dr Janeway, experiments were carried out to ascertain what effects changes in the caliber of the smaller blood vessels have on blood and plasma volumes. Volume determinations were made on dogs attached to a kymograph. The tracings with the blood values appear in Figures 1 and 2. The vasoconstriction was obtained by continuous administration of epinephrin, a fairly constant level being maintained for five minutes. In each determination, before injecting the dye, plasma was removed for the standard and within five minutes after the injection the samples were withdrawn for the volume estimations. The dogs weighed 14.3 and 12.7 kg respectively.

No striking change in blood or plasma volume accompanied the fairly marked variations in blood pressure. However, these blood pressure changes were of short duration.

Dr P. D. Lamson,^a working in Dr Abel's laboratory, has found that the polycythemia which develops after epinephrin injection does not reach its maximum for from fifteen to twenty minutes. Volume determinations made on two dogs after this interval showed a slight but definite decrease in plasma volume.

^a Personal communication.

Figure 1

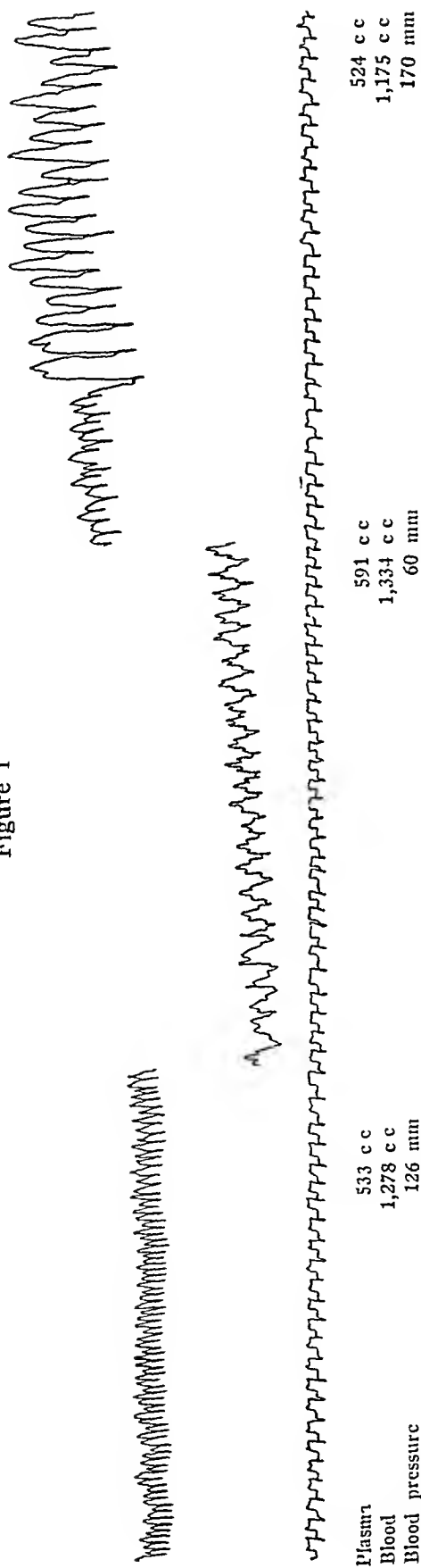
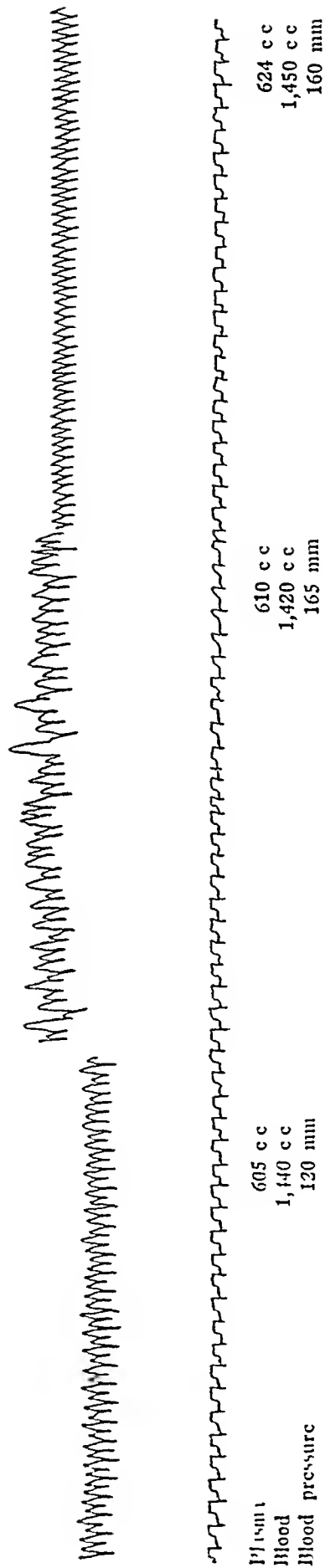


Figure 2



METHODS PREVIOUSLY EMPLOYED AND VALUES OBTAINED

According to Welcker,¹⁰ the earliest attempt to determine the blood volume was made by Haller¹¹. It consisted of bleeding two criminals to death, the amounts of blood obtained being 28 and 39 pounds.

The methods fall into two general groups, only those of Group 2 being applicable for clinical purposes.

1 *Direct Method*—Welcker, in 1854, bled animals to death, washed out the blood vessels with water, minced and washed the tissues thoroughly, brought the blood and washings together and determined their hemoglobin content. He concluded that the blood constituted one-thirteenth of the body weight in mammals. Shortly after this, Bischoff¹² applied this method to two criminals and obtained the same value. Modifications of the method were made by Heidenhain¹³ and by Plesch¹⁴. A similar preliminary procedure was used by Cohnstein and Zuntz,¹⁵ the calculations being based on cell counts instead of hemoglobin estimations, and by Kottmann,¹⁶ who employed the hematocrit.

2 *Indirect Methods*—A. Infusion method (a) Herbst,¹⁷ in 1822, injected the vascular system of a corpse until the vessels seemed moderately filled. (b) Vierordt¹⁸ experimented on animals. He determined the amount of blood pumped from the heart in one second and multiplied this by a number corresponding to the seconds required for a complete circulation. On the basis of certain calculations, he concluded that in man the blood constituted one-thirteenth of the body

10 Welcker, H. Bestimmungen der Menge des Körperblutes und der Blutfarbekraft, sowie Bestimmungen von Zahl, Maass, Oberfläche und Volumen des einzelnen Blutkörperchens beim Thier und beim Menschen, Prager Vrtljschr, 1854, iv, 11, Ztschr f rat Med, 1858 iv, 145.

11 Quoted from Welcker (Note 10).

12 Bischoff, L. W. Bestimmung der Blutmenge bei einem Hingerichteten, Ztschr f Wissensch Zool, 1856, vii, 331, Abermalige Bestimmung der Blutmenge bei einem Hingerichteten, ibid, 1858, ix, 65.

13 Heidenhain. Ueber die Blutmenge der Säugethiere mit besonderer Rücksicht auf Welcker's Methode der Blutbestimmung, Arch f physiol Heilk, 1857, n f, i, 507.

14 Plesch, J. Hamodynamische Studien, Ztschr f exper Path u Therap, 1909, vi, 380.

15 Cohnstein and Zuntz, N. Untersuchungen über den Flüssigkeits-Austausch zwischen Blut und Geweben unter verschiedenen physiologischen und pathologischen Bedingungen, Arch f Physiol (Pfluger's), 1888, xlii, 303.

16 Kottmann, K. Ueber die Bestimmung der Blutmenge beim Menschen und Tier unter Anwendung eines neuen Präzisionshaematokriten, Arch f exper Path u Pharmacol, 1906, liv, 356.

17 Quoted from Welcker.

18 Vierordt, K. Das Abhängigkeitsgesetz der mittleren Kreislaufzeiten von den mittleren Puls-frequenzen der Thierarten, Arch f physiol Heilkunde, 1858, n f ii, 527.

weight (c) ✓Valentin¹⁹ removed a definite amount of blood (a), then injected a known amount of water into the vascular system and bled again (b) The solids of a and b were determined, the difference being due to the number of cubic centimeters of water injected ✓Weber and Lehmann,²⁰ utilizing this method, concluded that the blood constituted one-eighth of the body weight (d) ✓Quincke²¹ utilized the method of ✓Mallassez²² Red counts were made in cases of pernicious anemia A known amount of blood with a known cell count was transfused, following which the patient's red cells were again counted From these data, the volume was calculated

B Inhalation Method ✓Gréhant and Quinquaud²³ gave dogs by inhalation a measured volume of carbon monoxid and determined its percentage content in a small sample of the animal's blood ✓Haldane and Smith²⁴ modified this method and applied it clinically The patient breathes for five minutes a measured quantity of carbon monoxid from a specially devised apparatus A sample of blood is removed and its carbon monoxid content estimated by the carmin titration method of Haldane ✓Plesch²⁵ and Oerum²⁶ have employed this method, but the former determined the carbon monoxid volumetrically

C Antitoxin Method Behring²⁷ noted that tetanus antitoxin remained in the circulation for long periods and made this the basis for the estimation of blood volume His studies showed the blood to constitute 1/118 of the body weight With it, Kammerer and Waldmann²⁸ in Muller's clinic, obtained a value of 1/102, while Fries²⁹ found a value of 1/126

19 Valentin, G Lehrbuch der Physiologie, ✓1847, 1, 493

✓20 Weber, E, and Lehmann, C G Lehrbuch der physiologische Chemie, 1850, II, Auflage II, 259

21 Quincke Weitere Beobachtungen über perniziöse Anämie, Deutsch Arch f klin Med, 1877, xx, 27, ref Plesch

22 Malassez, L Nouveaux procédés pour apprécier la masse totale du sang, Arch de physiol norm et path, 1874, vi, Série 2, 797

23 Gréhant and Quinquaud Mesure du volume de sang contenu dans l'organisme d'un Mammifère vivant, Compt Rend Acad Sc 1882, xciv, 1450

24 Haldane, J, and Smith, J Lorrain The Mass and Oxygen Capacity of the Blood in Man Jour Physiol, 1899-1900, xxi, 331 Smith, J Lorrain Discussion on the Blood in Disease, Trans Path Soc, London, 1900, li, 311

25 Tarchanoff, J R Die Bestimmung der Blutmenge in lebenden Menschen, Arch f Physiol (Pflüger's), 1880, xxi, 548 1881 xxiv, 525

✓26 Oerum, H P T Quantitative Blutuntersuchungen, Deutsch Arch f klin Med 1908, xciii 356

27 ✓Behring E Die Antitoxinmethode zur Blutmenge Bestimmung, München med Wchnschr, 1911, lvi 655

28 Kammerer H and Waldmann A Blutmengebestimmungen nach ✓Behring und andere quantitative untersuchungen der Blutbestandteile Deutsch Arch f klin Med, 1913 cix 524

29 Fries H Ueber Veränderungen der Blutmenge in Schwangerschaft Geburt und Wochenbett Ztschr f Geb u Gyn 1911, lxi 340

Table 4 indicates the wide variations that have been obtained by the different methods. The total number of normal cases has been small. In the report of Haldane and Smith,²⁴ the limits for normal are very wide. They state specifically, however, that one of the cases was very obese, that is, the one in which the blood was only one-thirtieth of his body weight.

TABLE 4—VARIATIONS IN BLOOD VOLUME BY DIFFERENT METHODS

Author	Method	No of Cases	Extreme Fractions	Average	Per Cent Body Weight	Remarks
Haller	Bled to death, weight of blood	2				24.30 pounds of blood. Body wt not given.
Welcker and Bischoff	Bled and washed out vessels of criminals. Compared with hematin	3	1/14 6 1/12 4	1/13	7.6	This was accepted standard from 1858 to 1881.
Tarchanow*	Sweating and counting R B C and Hb before and after steam bath	7	1/11 7 1/21 8	1/15	6.6	
Vierordt	No c.c. put out by heart multiplied by No. of seconds required for complete circulation			1/13		Worked on horses and dogs. Error, 12½ per cent.
Weber and Lehmann	Infused water, washed out vessels, determined dry substance of blood	2		1/8	12.5	
Haldane and Smith	CO inhaled. Carmin titration	12	1/30 1/16	1/21	3.34 6.27	
Kottmann †	Infusion of salt sol and hematocrit before and after	4	1/11 5 1/13	1/12.2	8.2	
Smith ‡	CO method. Titration with carmin solution	6 women 12 men			4.4 6.1 3.3 6.27	
Oerum	CO method. Titration with carmin solution	9 men 4 women			3.7 8.3 2.5-6.6	
Plesch	1. Infusion with Hb determinations 2. CO inhalation with combustion	21 4	1/21 1/16 5 1/20 1/16 5	1/19 1/18	4.69 6.05 5.02 6.05	15 % error
Kammerer and Wildmann	Behring method	7	1/11 1 1/9 3	1/10.2	9.10 7	
Fries	Behring method	10	1/17 5 1/11	1/12.6	7.9	Other practically normal patients gave similar values.

* Arch. f. physiol., 1880, xxii, 548, 1881, xxiv, 525.

† Arch. f. exper. Path. u. Pharmacol., 1906, liv, 356.

‡ Tr. Path. Soc. London, 1900, li, 311.

§ c.c. per 100 grams of body weight.

NORMAL AND PATHOLOGICAL VARIATIONS IN BLOOD AND PLASMA
VOLUME IN MAN

Results (Normal)

At least 140 determinations for plasma volume have been made on more than 100 individuals. In the earlier work, hematocrit studies were not made, so that the values for total blood volume are considerably fewer.

Normal Values—The results here reported are for normal men, being obtained from patients attending the outpatient department of the genito-urinary clinic for some minor local condition, such as chronic urethritis, chronic prostatitis or verumontanitis, etc. The age, weight, height and blood pressure, as well as the blood values, will be seen in the accompanying tables (5 and 6).

TABLE 5—PLASMA VALUES IN TWENTY-FOUR SUBJECTS

No	Name	Date	Age	Weight, Kg	Height, Ft In	B P Sys- tolic	Volume, cc	Ce per Kg	Frac- tion Body Weight	Per Cent Body Weight
1	F J	1/2	39	58.8	5 3	125	3,100	45	1/21.6	4.6
2	E M	1/6	22	69.5	5 10		2,775	47	1/20.7	4.8
3	G P	1/7	40	56.1	5 6	115	3,050	53	1/18.3	5.4
4	M	1/7	39	51.8	5 11		2,700	52	1/18.6	5.3
5	P	1/9	34	73.5	5 3	138	3,050	42	1/23	4.3
6	V	1/9	23	58.6	5 7	90	3,050	52	1/18.6	5.3
7	O	2/2 2/4		53.4 53			2,925 3,025	55 57	1/17.6 1/17	5.6 5.8
8	F	2/2 2/4		67 67			2,975 3,030	43 45	1/22 1/21.6	4.5 4.6
9	S	1/29	25	68.4	5 6		3,100	45	1/21.6	4.6
10	H S	12/28	33	58.9	5 5	90	2,975	50	1/20	5
11	P B	12/28	51	72	5 6	122	3,275	45	1/21.6	4.6
12	J J	12/28	22	57.5	5		2,800	49	1/19.8	5
13	J S	12/28	46	63.6	5 3	142	3,075	48	1/20.4	4.9
14	J C	12/29	43	71	5 6	130	3,325	48	1/20.4	4.9
15	H O	12/29	30	71	5 10		3,150	45	1/21.6	4.6
16	B S	12/31	32	65.3	5 6	145	3,100	47	1/20.7	4.8
17	G D	12/31	36	62.5	5 10	120	3,100	50	1/20	5
18	G	1/2	34	69.1	5 8	120	3,500	45	1/20.4	4.9
19	F L	1/2	32	59.9	5 5	105	2,500	49	1/19.8	5
20	F S	12/30	49	66.8	6	130	3,200	48	1/20.4	4.9
21	F J	1/5		70.5	6 2		3,750	53	1/18.2	5.4
22	J M S	3/11 3/12		52.3 52.5			2,675 2,675	51 51	1/19 1/19	5.2 5.2
23	D	1/22		70.9	5 11	120	3,075	48	1/20.4	4.9
24	S	1/12		56.4	5 7		2,825	50	1/20	5

TABLE 6—BLOOD VALUES IN EIGHTEEN NORMAL SUBJECTS

No	Name	Age	Date	Weight, Kg	Plasma Volume, cc	Cc per Kg Body Weight	Fraction Body Weight	Per Cent Body Weight	Hematocrit		Total Blood Volume	Cc per Kg Body Weight	Fraction Body Weight	Per Cent Body Weight
									R B C	Plasma				
25	H G		3/11/15 3/12/15	64.3 64.3	3,175 3,075	49.4 48	1/20 1/20.4	5 4.9	38.3	61.7	5,125	79	1/12	8.3
26	J T	36	4/24/15	85	3,775	44	1/22	4.5	43.4	56.6	6,675	78.5	1/12	8.2
27	W	21	4/24/15	76.3	3,525	46	1/21	4.7	44	56	6,300	82	1/11.6	8.6
28	H S		5/ 7/15	61.8	3,225	52	1/19	5.3	45.4	54.6	5,900	95	1/10.5	9.9
29	W		4/21/15	59.5	2,975	50	1/20	5.1	37.6	62.4	4,775	80	1/12	8.4
30	W-t	53	5/ 3/15 4/22/15	65.3 63.5	3,400 3,375	52 53	1/18.3 1/18.3	5.3 5.4	41.6 40	58.4 60	5,775 5,625	88 88	1/11 1/11	9.2 9.2
31	B	26	4/28/15	63.6	3,025	48	1/20.4	4.9	48	52	5,825	92	1/10.4	9.6
32	J	24	4/23/15	56.8	2,850	50	1/20	5.0	45.7	54.3	5,250	92	1/10.4	
33	G		4/28/15	60.9	3,300	54	1/17.9	5.5	40.5	59.5	5,500	91	1/10.4	9.5
34	L	28	4/28/15	60.7	3,200	52	1/18.3	5.3	46.9	53.1	6,025	99	1/19.6	10.4
35	E	20	4/28/15	72.5	3,575	49	1/20	5.0	38.6	61.4	5,825	80	1/12	8.4
36	L	21	5/ 2/15	66.5	2,874	43	1/22.7	4.4	49	51	5,725	84	1/11.4	8.8
37	H B	23	5/ 3/15	47.4	2,850	52	1/18.4	5.3	43	57	4,200	88	1/11	9.2
38	R K	25	5/ 3/15	72.3	3,300	46	1/21.3	4.7	45	55	6,000	83	1/11.5	
39	J O	33	5/15/15 5/ 7/15	55.5 56.8	2,775 2,850	50 50	1/20 1/20	5 5	45 40.4	55 59.6	5,025 4,775	90 84	1/10.5 1/11.4	9.4 8.8
40	G P	40	1/ 7/15	56.1	3,040	53	1/18.5	5.4	32.7	67.3	4,525	80	1/11.9	8.4
41	W M	39	1/ 7/15	51.8	2,700	52	1/18.7	5.3	38.2	61.8	4,375	84	1/11.3	8.8
42	I M	22	1/ 6/15	69.5	3,275	47	1/20.8	4.8	42.9	57.1	5,725	82	1/11.5	8.7

Plasma Values—Forty-eight determinations were made on forty-two patients. The largest (3,775 cc) and smallest (2,450 cc) volumes were encountered in the heaviest (85 kg) and lightest (47.4 kg) patients (Nos. 26 and 36 respectively). The mean weight was 61.2 kg and the mean volume 3,125 cc, the average weight, 63.3 kg and the average volume 3,050 cc. The plasma varied from 42 to 56 cc per kilogram, while the fraction of body weight varied from 1/23 to 1/17, the average being 1/19.4. (From this it appears that a normal man of 140 pounds has 3 liters of plasma, or 50 cc per kg.) The constancy in the relation of plasma to body weight in health is striking, there being no great extremes.

Blood Values—The number of determinations of total blood values has not been so large. Twenty-one determinations on eighteen normal individuals were made, the whole blood values being calculated from the plasma volume and hematocrit findings. The plasma constitutes on the average 56.9 per cent of the total blood, the extremes being 51 per cent and 62.6 per cent. The largest and smallest volume (6,675 cc and 4,200 cc) were obtained in the two patients mentioned above as having the largest and smallest plasma volumes. These patients showed 78.5 and 97 cc per kilogram, respectively. The average blood volume was 5,350 cc, or approximately 85 cc per kilogram. On a gravimetric basis, the blood constituted 8.8 per cent, or 1/11.4 of the body weight. The variations in health were not great—from 1/13 to 1/10.5 of the body weight.

The constancy of these values is in striking contrast to those of Haldane and Smith²⁴ and of Oerum,²⁶ who found the blood-body-mass relationship exceedingly variable. The results here reported support the figures of Welcker and Bischoff, Vierordt, Kottmann, Behring, Fries, and Kammerer and Waldmann.

Clinical Studies (Pathological)

Sixty-five patients were studied, the determinations numbering eighty-eight.

For purposes of discussion the cases are grouped according to clinical conditions. It is to be regretted that the number of cases in each group is not larger. This was impossible, since the drug is of German origin and despite repeated efforts it was impossible to secure a further supply.³⁰ The scope of the work has been limited by the small amount of dye available.

³⁰ It is probable that many dyes will answer the purpose equally well. Studies using these dyes are now in progress.

TABLE 7—BLOOD OBSERVATIONS BEFORE AND AFTER DELIVERY

No	Name	Age	Para	Relation of Observation to Labor, Days		Blood Lost	Weight of Child	Body Weight	Plasma Volume	O c per Kilo	Blood Volume	Per Cent of Body Weight	Per Cent of Estimated Weight	Estimated Decrease in Blood Volume	Hematocrit Volume R B C
				Before	After										
1	L V	21	0	2	5	210	4,165	55.5 48.2	3,213 2,487	57.9 51.6	5,637 4,363	10.66 9.50	11.16	1,275	43 43
2	G Z	30	1	19	4 11	100	4,150	61 52.7 53.9	3,343 3,057 2,641	54.8 58 49	5,306 4,700 4,192	9.13 9.36 8.1	10	506 1,286	37 35 37
3	M B	16	0	13	4	150	3,315	51.8 45.4	2,621 2,243	50.6 49.4	3,971 3,299	8.05 7.6	8.5	672	34 32
4	E J	20	0	9	1½ 9	325	3,100	57 50 50.5	3,329 3,030 2,525	58.4 60.6 50	5,014 4,734 3,915	9.03 9.94 8.2	9.6	310 1,099	34 36 36
5	O O	23	3	6	4	250	3,970	65.6 55	3,870 2,695	59 49	5,691 4,022	9.11 7.63	9.7	1,569	32 33
6	F S	25	2	4	3	800	3,085	63.9 57.3	3,623 2,974	56.7 51.9	6,039 4,721	9.92 8.65	9.5	1,318	40 37
7	E T	22	1	39	9	200	4,075	64.5 60	4,689 3,078	72.7 51.3	7,105 4,809	11.55 8.41	12.5	2,296	36
8	L L	22	2	4	7	100	3,640	61.4 59.3	3,899 2,894	63.5 48.8	5,262 4,904	8.98 8.68	10.2	358	28 41
9	B W	18	0	11	5	225	3,420	61.7 59.1	2,974 2,216	48.2 37.5	4,647 3,821	7.89 6.79	9.4	826	36 42
10	A McD	20	0	1	8	675	3,420	63 57	3,717 2,519	59 44.2	6,300 3,760	10.5 6.9	11.4	2,640	41 43
11	M F	16	0	6	10	200	1,040	47.1 43.6	1,795 1,548	38.1 35.5	3,042 2,669	6.78 6.43		373	41 42
12	E Z	17	0	61				54.5	3,461	63.5	5,408	10.42			36
13	M	19	0	14?				57.3	3,266	57	5,184	9.51			37

Pregnancy—Observations have been made before and after delivery in eleven cases (Table 7) In the latter months of pregnancy, the blood mass in proportion to the body weight is definitely increased Whereas, normally, blood constitutes 88 per cent, in twelve pregnant women prior to labor the blood averaged 956 per cent, which corresponds to the highest limits of normal value In four instances, the blood values rose considerably above normal limits The plasma volumes were correspondingly increased, averaging 584 c c per kilogram, instead of 50 c c Determinations made a week to ten days after labor showed that a great decrease in the blood mass had occurred which could not be accounted for by loss of weight (child, placenta and amniotic fluid) or loss of blood at parturition After labor, the blood and plasma formed 9 per cent and 49 per cent of the body weight, respectively The average loss of blood, according to the obstetrical report of these cases, was only 300 c c, whereas blood volume studies showed an average loss of 1,100 c c

Efforts have been made, but without success, to find the dye in the placenta, in the amniotic fluid and in the child's urine, following the administration of the dye intravenously to the mother during labor Abnormal absorption of the dye would not seem to be the explanation of the high blood values recorded in pregnancy This opinion is based on the fact that the decrease in blood mass is not found immediately after parturition, for in two cases (2 and 4) it will be seen that determinations made thirty-six hours in one case, and four days after delivery in the other, showed the same high values for plasma and blood Subsequent determinations, ten days after labor, showed in both cases the marked decrease recorded in the other cases of the series The consideration of blood volume in relation to pregnancy will form the subject of a separate communication in collaboration with Dr J R Miller, with whom this part of the work was carried out in the wards of Prof J Whitridge Williams

These findings confirm the widespread belief among obstetricians that pregnant women stand hemorrhage unusually well Comparatively very large bleedings in eclampsia are well borne It would appear that Nature has here a factor of safety, the large blood volume, safeguarding against the effects of hemorrhage before during or after labor Or it may be that the larger blood supply is necessary for proper nutrition of the child

Case 11 was complicated by secondary lues and nephritis It does not accord with the other cases of the series

Emaciation—Two cases (1 and 2, Table 8) are included. The first is in a woman who had lost 12 to 15 kg through voluntary starvation. The plasma volume is absolutely normal, and since red cells were 4,000,000, her blood volume was, in all probability, not much below normal. The second patient, very tall and thin, also showed strictly normal values.

Obesity—Six cases (Nos 3, 4, 22, 26, 31 and 32, Table 8) showed in every instance a plasma volume decidedly below that of the average normal. The average was 37.1 cc per kg, or 3.8 per cent of body weight, which is less than three-fourths of the normal value. In the one case (32) in which a hematocrit reading was obtained, 51 cc per kilogram of blood was found. This patient had only as much blood per kilogram as the normal individual has plasma per kilogram. Case 3 is of extreme interest, inasmuch as the plasma formed less than 3 per cent of the body weight. These findings are in harmony with those of Haldane and Smith.

Emaciation and Anemia—Ten cases (Nos 5 to 14, inclusive, Table 8) exhibiting emaciation, in combination with moderate or severe secondary anemia, were studied. In three of these, malignant neoplasms were present. In six, the plasma volume was higher than the average normal, and in three, abnormally high. The average in eight cases was 56 cc per kilogram, which indicates a serous plethora. In four, the total blood volume was studied and three gave low values. It is evident, therefore, that in such conditions loss of plasma does not go hand in hand with loss of weight and decrease of red blood cells. Unfortunately, hematocrit studies were not made in the carcinoma cases. With the degree of anemia indicated in the table, it is evident, however, that the total blood volume must have been approximately normal.

Since the average blood value was 78 cc (1/13.2 of body weight), instead of 85 cc per kg, it becomes apparent that the anemia is fairly accurately indicated by the blood count. In Cases 8 and 11, there is a decrease in the volume, as well as in the cell content of the blood.

Pericious Anemia—Only three cases (Nos 15, 16 and 17, Table 7) were studied. No 15 showed an extremely high plasma volume of 72 cc per kg, the highest encountered outside of pregnancy. The blood volume was normal, but slightly below the average. In the other two, plasma values were normal, and the total volume considerably decreased.

With so great an increase in plasma volume in Case 15, it was thought that the whole blood mass might be larger than normal and be brought into causal relationship with the enlarged heart sometimes

seen in pernicious anemia. The two subsequent cases showed low blood values and no cardiac enlargement. Further data in this connection are necessary.

Polycythemia—Only two cases (Nos 18 and 19, Table 8) with high blood counts were studied. Patient 18, throughout several weeks' stay in the wards, presented a persistently high red cell count (8,000,000). Two determinations, a week intervening, yielded identical results, that is, both plasma and blood volumes were decidedly smaller than normal. This patient cannot, therefore, be considered plethoric, since he has only 73 c c of blood per kg, instead of the normal 85 c c per kg. The total number of cells and the absolute hemoglobin were probably about normal. The apparent plethora was caused by the low plasma content of the blood, 39 c c instead of 50 c c per kg.

Patient 19 showed a red blood cell count of 5,600,000, a count slightly above normal. This is an instance of true plethora. The plasma volume was also considerably above the average normal, being 60 instead of 50 c c per kilogram. The blood pressure was 135/90, while the blood was 113 c c per kilogram, instead of 85 c c per kilogram.

These cases strikingly demonstrate the necessity of total value for the proper interpretation of the routine methods of studying the blood.

Three other cases showed counts somewhat above the normal. In two of these, the plasma volume was low and the blood volume consequently not increased.

Diabetes—Of the four patients whose cases were studied (Nos 20 to 23, inclusive, Table 8), three were moderately thin men and one an obese woman. The three men showed a sugar content in the blood between 0.18 per cent and 0.45 per cent, and all showed plasma and blood volumes that were strictly within the limits of normal. The obese patient (No 22) showed blood volume decidedly below normal, so that the obesity exerted a greater influence on the blood-body-mass relationship than did the glycosuria. From these four cases it appears that an increase in the blood volume does not result from or accompany hyperglycemia.

Myocardial Insufficiency—Nine plasma determinations were made on seven cases (Nos 24 to 30, inclusive, Table 8) of myocardial insufficiency. Nephritis was absent or played a very minor rôle in this series. Several of these patients had marked edema, and the average volume, 47 c c per kilogram, was slightly low, so that, in general, edema is not associated with an increase in plasma corresponding to the increase in weight. High values may occur, as is seen in Patient 30. The lowest plasma value (Case 27) is associated with a high red blood count.

TABLE 8—CLINICAL (PATHOLOGICAL)—

No	Name	Date	History No	Age	Diagnosis	Red Blood Cells	Hgb Sahli	Weight	
								Actual	Best
1	A E	1/15	33581	32	Chronic pancreatitis Malnutrition	4,022,000	82	36 8	48
2	E J	1/5	33514	24	Visceroptosis Accident Pain in side	5,100,000	100	70 5	
3	R M	1/15	33583	48	Syphilis Obesity	4,200,000	84	95 4	100
4	E N	1/6	33506	58	Obesity Myocardial insufficiency, hypertension	5,000,000	80	107 7	159
5	R B	1/6	33467	66	Carcinoma stomach	2,600,000	45	38 8	
6	J H C	1/12	33559	72	Achylia gastrica, malnutrition	4,000,000	80	52 7	68
7	J H	1/6	33474	65	Arteriosclerosis Carcinoma prostate Metastases	2,120,000	45	48 6	
8	A E	3/18	33818	31	Secondary anemia Diarrhea	3,600,000	61	43 9	527
9	J N	1/15	33586	48	Psychosis Migraine Carcinoma stomach	3,800,000	65	55 9	68
10	H W	4/9		25	Balantidium coli Secondary anemia	1,072,000	20		
11	J S		33040	22	Secondary anemia Leg ulcers	1,500,000	31	50	
12	R A	1/8	33522	54	Anacidty Malnutrition Secondary anemia	4,600,000	70	44 5	75
13	F M	3/12	33829	39	Duodenal ulcer Secondary anemia	3,500,000	75	59 5	70
14	P S	2/22	33714	34	Acute nephritis Syphilis Secondary anemia	3,500,000	65	63	87
15	P J B	1/5	33433	42	Pernicious anemia	1,192,000	28	68 2	
16	T A	2/25	33770	38	Pernicious anemia	1,500,000	25	64 1	
17	W M	1/23	C H I	69	Pernicious anemia Aplastic type	1/17, 1,300,000, 1/28, 800,000	22 15	53 6	
18	G T	2/17 2/25	33642	22	Peritoneal adhesions Polycythemia	8,000,000	100	50 5	55
19	F O	1/5	33526	25	Mitral insufficiency Left hemiplegia	5,600,000	101	69 1	72
20	G V H	3/18	33876	23	Diabetes mellitus Pulmonary tuberculosis Coma	5,400,000	98	42 5	53
21	E N V	3/11	33787	60	Diabetes mellitus Pulmonary tuberculosis Arteriosclerosis	4,700,000	82	58 2	76
22	M B J	1/21	33487	37	Aortic insufficiency Diabetes mellitus Obesity		85	80 9	80
23	L W	3/12	33817	29	Diabetes mellitus	5,500,000	89	54 1	67
24	B S	1/12	33571	44	Myocardial insufficiency Pulmonary tuberculosis	5,200,000	100	75 2	84
25	O O M	2/17 2/25	33735	60	Arteriosclerosis Myocardial insufficiency	4,700,000	94	87 3 73 4	
26	W J R	1/15	33584	70	Myocardial insufficiency	5,000,000	84	89 5	
27	J S	1/6	G No 98729	48	Syphilis Aortic insufficiency myocardial insufficiency	6,500,000	107	68 8	
28	W	1/23			Myocardial insufficiency			73 2	
29	J S M	1/9	33521	59	Arteriosclerosis Angina pectoris Myocardial insufficiency	5,000,000	80	89 5	112
30	J F	1/12 1/22	33531	42	Syphilis of aorta Aortic insufficiency			60 4 59 1	
31	E W S	2/4	33679	62	Pulmonary tuberculosis Arteriosclerosis Chronic nephritis	5,000,000	75	90 2	

—STUDIES ON BLOOD VOLUME

Edema	Blood Pressure	Cardiac Enlargement	Plasma c c	O c Per Kg	Hematocrit Per Cent Plasma	Blood Volume *	O c per Kg	Per Cent Body Weight	Fraction Body Weight	Remarks
None	100/60	None	1,850	50						
None	120/80	None	3,750	53	60	6,250	89	9.3	1/10.9	6 feet 3 inches in height
None	120/70	None	2,725	28.6						
Slight	210/110	Moderate	4,950	45.8						
None	100/60	None	2,575	66	75	3,425	88	9.2	1/10.8	
None	150/100	None	2,375	45						
Right leg anurum	130/65	None	3,150	64	77.2	4,075	84	8.8	1/11.4	
None	100/65	None	2,175	49	65.3	3,325	76	8	1/12.5	
None	110/65	Slight	3,725	66						
Moderate	105/45	Slight	3,425	60	85.6	4,025	70	7.3	1/13.6	
None		None	2,900	57	78.8	3,675	72	7.5	1/13.2	
None	120/90	Slight	2,120	47.6	67.3	3,150	71	7.4	1/13.5	
None	100/65	Slight	3,400	57	70.6	4,800	88	9.2	1/10.8	
None	120/75	Slight	3,225	51	64.3	5,025	80	8.4	1/12	
None	100/55	None	4,950	72	90	5,500	81	8.5	1/11.7	
None	120/70	Slight	3,450	54	84	4,250	66	6.9	1/14.4	Improved
None		None	2,850	53						Died
None	120/70	None	1,975	39	53.2	3,725	73	7.7	1/13.5	
			2,000	39	53.2	3,750	73	7.7	1/13.5	
None	135/90	Slight	4,125	59.7	52.5	7,880	113	11.9	1/8.4	
None	140/90	None	2,175	51.3	57	3,800	89	9.3	1/10.7	Blood glucose 0.25-0.3
None	160/60	Slight	3,275	36	62.1	5,375	92	9.6	1/10	Necropsy Blood glucose 0.45-0.18
None	120/70	None	2,825	35						Blood glucose 0.18
None	120/80	None	2,775	51						Blood glucose 0.4-0.34
Marked	90/50	Moderate	3,900	50						
Marked	120/80	Marked	4,375	50	54.3	8,050	92	9.6	1/10.3	Necropsy
Slight		Marked	3,900	53						
Moderate	170/120	Moderate	3,800	42.5						
Moderate	150/90	Marked	3,025	49	45.6	6,670	87	9.1	1/11	
			3,175	43						
Moderate	150/115	Marked	3,975	40						Necropsy
Slight	120/90	Slight	3,355	76						Necropsy
	115 "		2,811	48						
Slight	105/60	Slight	2,200	50.7						Weight 120 lbs In 1907

TABLE 8—CLINICAL (PATHOLOGICAL)—

No	Name	Date	History No	Age	Diagnosis	Red Blood Cells	Hgb Sahl	Weight	
								Actual	Best
32	L J		33777	47	Hypertension Chronic nephritis	5,000,000	90	79 4	
33	E F	1/20	33757	36	Osteo arthritis of spine Syphilis Arteriosclerosis Hyper- tension Chronic nephritis	3,500,000	65	62 3	65
34	E O	2/21	33697	47	Arteriosclerosis Chronic neph- ritis Hypertension Poly- cythemia	5,900,000	105	72	80
35	G L	1/20	33510	53	Syphilis Hypertension	5,000,000	83	60 7	70
36	R A	2/17	33643	45	Chronic nephritis Hypertension Myocardial insufficiency	3,000,000	60	65 9	
37	F W	2/17	33722	47	Chronic nephritis Hypertension Cerebral hemorrhage	5,800,000	92	56 6	
38	M C	1/23	C H I		Hypertension			42 7	
39	J E A	2/12	36283	49	Chronic nephritis Hypertension Arteriosclerosis Hematuria	a m, 4,000,000, p m, 3,700,000	80 75	78 3 76 4	
		2/18						75 9	
		2/25						70 1	
40	H O C	1/14	36082	55	Arteriosclerosis Hypertension Enlarged prostate			98 4	
41	N P P	3/18	36551	51	Arteriosclerosis Hypertension Carcinoma of bladder	3,800,000	72	59 1	
42	E S H	2/12	36298	71	Arteriosclerosis Hypertension			87 3	
43	M P	1/12	33549	32	Chronic nephritis Hypertension Myocardial insufficiency	4,400,000	63	76 3	
44	W L I	1/12	33424	38	Chronic nephritis	4,000,000	82	80 9	
		2/3						79 5	
45	T K	1/12	33544	29	Chronic nephritis	4,200,000	93	62 7	73
46	A T	1/3	33472	22	Chronic prostatitis	4,300,000	100	52 3	61
47	T W	1/7	33479	71	Chronic infectious arthritis	4,800,000	75	72 7	73
48	R K S	1/12	33572	51	Cerebral arteriosclerosis Brain tumor?			56 4	
49	F N	1/20	33390	40	Emphysema Chronic bronchitis	5,000,000	90	54 8	
50	B	1/7	33333	43	Syphilis Aneurysm of thoracic aorta	4,200,000	92	61 4	
		2/2						63 6	
51	F T	1/14	33345	53	Chronic appendicitis	5,000,000	90	48 6	
52	M	1/14	33461	18	Typhoid fever	4,500,000	85	60	
53	S B	2/27	36426	49	Carcinoma bladder Secondary anemia	3,300,000	33	58	
		3/11						58 4	

STUDIES ON BLOOD VOLUME—(Continued)

Edema	Blood Pressure	Cardiac Enlargement	Plasma c c	O c Per Kg	Hematocrit Per Cent Plasma	Blood Volume	O c per Kg	Per Cent Body Weight	Fraction Body Weight	Remarks
Slight	180/100	Moderate	2,700	34	66.7	4,050	51	5.3	1/18.7	
None	200/150	Slight	3,050	49						
.			3,150	51						
None	200/150	Slight	3,050	42	56.1	5,475	76	8	1/12.5	Blood glucose 0.12
.				48	61	5,675	78	8.2	1/12	
None	185/105	Slight	3,025	50						
Slight	240/130	Slight	3,175	48	63	4,913	74	7.8	1/12.7	Blood glucose 0.14 Died
None	195/130	Slight	2,950	52	54.3	5,425	96	10	1/10	
None	180/ ?	Slight	1,825	43						
None	245/140	Moderate	4,650	59						
.	235/135		3,875	51	63	6,150	84	8.8	1/11.9	800 c c blood removed
.	235/155		3,425	45	63	5,425	80	8.4	1/13.1	
	220/125		4,150	55	75	5,500	72	7.6	1/13.1	
None	175/110	Slight	3,500	50	60.8	5,750	81	8.5	1/11.7	
None	195/110	Slight	4,325	44	66.4	6,525	65	6.8	1/14.7	Died
None	210/ 90	Moderate	3,150	53						
Considerable	180/100	Marked	3,875	44	64.4	6,025	69	7.2	1/13.9	
Slight	115/ 75	Slight	4,047	53						
Moderate	130/ 80	Slight	3,172	39						
			3,064	38.4						
None	100/ 85	None	2,925	46						
None	140/ 90	Slight	2,420	45						
None	140/ 85	None	3,450	47.6	63.7	5,425	75	7.8	1/12.8	
None	120/ ?	Slight	2,825	56.4						
None	110/ 70	None	2,450	45						
None	120/ 70	Slight	3,025	49	60	4,000	78	8.1	1/12.2	
			3,175	50						
None	110/ 70	None	2,200	46						
None	95/ 60	None	3,050	50						
None	103/ 55	Slight	2,500	61	70.6	4,550	78	8.2	1/12.2	Died
			3,350	57						

Although in anasarca the number of cubic centimeters of blood per kilogram may not be increased above normal, the total blood volume may be large in relation to the normal body weight. Case 25 had a blood mass of over 8 liters. With the disappearance of his edema, he lost 14 kg. Considering his weight at this time in relation to the blood volume, 8,050 c c, found during edema, he had 109 c c per kilogram, which is an extremely high value. The patient died six weeks later. At necropsy, the kidney showed numerous small scars throughout, with some atrophy of the tubular cells, and also an acute inflammatory process, as evidenced by infiltration with polymorphonuclear leukocytes. There was a slight chronic nephritis with an acute terminal process. Myocarditis was extensive and fibrous in type, with hypertrophy of muscle and small scattered scars everywhere. The heart was of tremendous size. It is quite possible that in this instance the large blood mass stood in causal relationship to the large heart.

Hypertension and Chronic Nephritis—In nineteen determinations on thirteen cases (Nos. 31 to 43, inclusive, Table 8), a plasma volume greater than normal was found only once, while the total blood volume was not found increased in nine determinations on six cases. This would appear to demonstrate that in these cases the hypertension was not dependent on an increase in blood mass. In hypertension, the blood volume is normal and frequently low. The increased tension would appear, therefore, to be dependent on a vascular system that is too small, rather than on a blood volume that is too large. The average value for plasma was 42.8 c c per kilogram, and for the whole blood, 75 c c per kilogram, in both instances the lower limit of normal. The small values are not dependent on edema, as will be ascertained from the table, since in only three cases was even slight edema present, and in only one was there great cardiac enlargement. The results are in striking contrast with those of Plesch.¹⁴

Several of these cases are of peculiar interest. Patient 39, who, on one determination showed an increased plasma volume, had a marked hematuria so that hemorrhage may have accounted for this finding. Subsequent determinations showed the plasma volumes to be normal. Following venesection with removal of 800 c c, there was no decrease in blood pressure but immediate decrease in plasma volume. A week later, there was an increase in plasma to above that found before the venesection but without a corresponding increase in the blood volume.

That hypertension can exist in association with a low blood volume is clearly indicated by Case 32, the patient showing a systolic blood pressure of 180 and diastolic of 100. The plasma was 34 c c per kilogram and the total blood 51 c c per kilogram. The hypertension

existed despite the fact that the patient's total blood mass was not greater than the plasma volume is normally. Obesity and a slight edema were in part responsible for these low values.

Case 43 is also of great interest. The patient is the only one of the series presenting marked edema at the time of determination. At this time, he had 40 c c of plasma per kilogram. Following a loss of 11 kg (disappearance of edema), the plasma volume was found to be slightly larger, 4,050 c c, compared with 3,875 c c. It is evident that the plasma volume remained the same throughout, not being influenced by the presence or disappearance of the edema. This does not always occur, as will be seen by contrasting with Case 25.

From these cases, it would appear that true plethora is not present in hypertension, and that a small or contracted vascular system and not an increase in blood mass is responsible for the increased blood pressure.

Chronic Nephritis Without Hypertension—Only two cases (Nos 44 and 45, Table 8) fall into this group. Patient 44 was an instance of chronic parenchymatous nephritis, with slight edema and very marked albuminuria. The plasma was estimated twice, three weeks intervening. Following a 1.5 kg decrease in weight, the plasma decreased 100 c c. Both cases gave values below the normal average for plasma.

Miscellaneous Group—A small series of miscellaneous unrelated cases (Nos 46 to 53, inclusive, Table 8) were studied. Case 50, an instance of aneurysm of the ascending arch of the aorta, and with a moderate grade of anemia, showed identical results on two occasions—an average normal value for the plasma. Patients 49, suffering with chronic bronchitis, 51, with chronic appendicitis, 46, a neurasthenic, and 48, with cerebral arteriosclerosis, all showed values within the limits of normal.

COMMENT

Except in pregnancy, hypertension and obesity, the number of cases studied in any one condition has been so small that far-reaching conclusions are impossible. Sufficient evidence has been adduced to convince us of (a) an increase in blood volume just before term in uncomplicated pregnancy, (b) absence of a causal relationship between increased blood volume and hypertension, and (c) of a relatively small blood mass in obesity. Further blood volume studies in these and in other clinical conditions is contemplated.

From this study, it is apparent that a great variation in the blood mass in relation to body weight may occur in any one disease. Complications of any kind may also exert a great influence on the blood volume, as evidenced by Case 2 in Table 7. It becomes evident that

we cannot take for granted that the blood volume is increased or decreased in any given disease, but must actually determine it in each individual case. In the present state of the subject, generalizations are undesirable.

SUMMARY

1 A method for the determination of plasma volume is described. From the plasma volume and hematocrit values the blood volume can be calculated.

2 With this method, duplicate determinations on normal subjects yield identical values.

3 The amount of decrease in blood volume as the result of hemorrhage and of increase following intravenous infusion of saline has been demonstrated.

4 Changes in blood volume are insignificant in experimentally induced hypertension and hypotension, and cannot be brought into causal relationship with them.

5 The plasma normally constitutes approximately 5 per cent or one-twentieth of the body weight. Normal individuals have approximately 50 c c of plasma per kg, the extremes being from 42 to 56 c c per kilogram.

6 The normal hematocrit values obtained were approximately 43 per cent for erythrocytes and 57 per cent for plasma.

7 The blood normally constitutes 88 per cent, or 1/114 of the body weight. Normal individuals have approximately 85 c c of blood per kilogram, the extremes being 78 and 97 per kilogram.

8 In pregnancy, before term, the blood and plasma volumes are increased. A condition of serous plethora exists. Within a week or two after delivery, the blood values return to normal.

9 In obesity, the plasma and blood volumes are relatively small.

10 Many cases of anemia exhibit a relatively large plasma volume.

11 Polycythemia in the sense of a high blood count may be dependent on a low plasma volume. It may be associated with a large plasma volume, in which case true plethora is indicated.

12 Hyperglycemia exists without increase in blood volume.

13 In anasarca accompanying myocardial insufficiency the blood volume may be absolutely increased.

14 A small volume is shown in many cases of marked hypertension. Therefore so far as these studies go it would appear that hypertension is not dependent on a large blood volume.

STUDIES OF NITROGEN PARTITION IN THE BLOOD AND SPINAL FLUID

WITH ESPECIAL REFERENCE TO THE POSSIBLE CAUSATION OF
ALBUMINURIC RETINITIS *

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The fact that an albuminuric retinitis, occurring in the course of a chronic nephritis, is a sign of the gravest prognostic import, has long been recognized. Within the last five years, this has been the subject of considerable investigation, especially by the French clinicians, and several very interesting theories have been advanced. Chauffard¹ attempted to explain albuminuric retinitis on the grounds of a hypercholesteremia, while Onfrey and Balavoine² attempted to show that changes in the viscosity of the blood played an important part. The theory that attracted the greatest amount of attention, however, was that advanced by Vidal³ in 1910. He stated that albuminuric retinitis was the result of the retention in the blood of urea, or of some nitrogenous body closely allied to urea. In 1912 Vidal⁴ reviewed the work of Chauffard and agreed with him that cholesterol, lipoids, and lecithin compounds might often be retained in the blood in nephritis. Vidal found, however, that this retention fell as the urea retention rose and stated that retinitis occurred only in those cases which showed a definite nitrogen retention. The prognostic significance of albuminuric retinitis was due, therefore, he believed, to the fact that it stood as a sign of nitrogen retention.

The object of my work has been to determine whether such a relation between nitrogen retention and the occurrence of albuminuric retinitis could be demonstrated, and whether or not albuminuric retinitis could be charged to "urea or to any closely allied nitrogenous body." Using the newer methods, estimations were made of the total non-protein nitrogen, of the ammonia nitrogen, of the urea nitrogen, the

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¹ From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Chauffard. Pathogenie des retinites albuminuriques, *Semaine med*, 1912, XXXII, 193.

2. Onfrey and Balavoine. Viscosite du sang et hemorrhagies oculaires, *Ann d'ocul*, 1911, cxlii, 433.

3. Vidal, Morax and Weill. Retinite Albuminurique et Azotemie, *Ann d'ocul*, 1910, cxlii, 354.

4. Vidal, Weill and Lendat. La lipemie des brightiques, rapports de la retinite des brightiques avec l'azotemie et la cholesterinemie, *Semaine med*, 1912 XXXI 521.

uric acid, creatinin, combined creatinin and creatin, and of the amino-acid nitrogen in the blood. Estimations were also made of the total nonprotein nitrogen and urea nitrogen in the spinal fluid, taken at the same time.

In a review of the literature, the first important work on nonprotein nitrogen retention in the blood seems to have been done by von Jaksch⁵ in 1893. He gave figures for the nitrogen content of the alcoholic filtrate from blood, and showed there was a marked increase in the nonprotein nitrogen in the blood in chronic nephritis. H. Straus⁶ in 1902 gave figures in nitrogen partition, finding 75 per cent of the total nonprotein nitrogen as urea nitrogen, 24 per cent as uric acid, and 5 per cent as ammonia. In high nitrogen retention, he found these same figures held. Holweg⁷ in 1911, found 60.8 per cent of the total nonprotein nitrogen as urea nitrogen, 27.4 per cent as amino-acid nitrogen and 11.7 per cent as albuminose nitrogen. He found that as the total nonprotein nitrogen retention increases, the urea and amino-acid nitrogen increased proportionally, while the albuminose nitrogen remained stationary. Obermayer and Popper⁸ in 1911 reviewed the literature and cited the following results of investigation on the retention of nitrogenous bodies. Jaccoud⁹ thought creatin retention the cause of uremia. Coetbeer and Hunden¹⁰ found that in the great nonprotein nitrogen retention following extirpation of the kidney, urea nitrogen was only one-third the total. Oppler and Hoppe-Seyler¹¹ found creatinin increased in the blood in chronic nephritis, and von Jaksch¹² found an increase in uric acid. Obermayer and Popper themselves found nonprotein nitrogen in the blood in cases of uremia varying from 57 to 658 mg per hundred c.c. of blood, of which an average of 64 per cent was urea nitrogen.

Philipp¹³ in 1913 reported a series of cases giving the total nonprotein nitrogen and the urea nitrogen content in the blood in cases of uremia. Using phosphotungstic acid to precipitate the proteins in the determination of the total nonprotein nitrogen, he found the urea

5 Von Jaksch. Ueber die Zusammensetzung des Blutes gesunder und kranker Menschen, *Ztschr f klin Med*, 1893, xiii, 187.

6 Straus, H. Die chronischen Nierenentzündungen in ihrer Einwirkung auf Blutflüssigkeit, Berlin, 1902.

7 Holweg. Ueber das Verhalten des Reststickstoffes des Blutes bei Nephritis und Urämie, *Deutsch Arch f klin Med*, 1911, civ, 216.

8 Obermayer and Popper. Ueber Urämie, *Ztschr f klin Med*, 1911, lxxii, 332.

9 Jaccoud. Quoted by Obermayer and Popper, Note 8.

10 Coetbeer and Hunden. Quoted by Obermayer and Popper, Note 8.

11 Oppler and Hoppe-Seyler. Quoted by Obermayer and Popper, Note 8.

12 Von Jaksch. Quoted by Obermayer and Popper, Note 8.

13 Philipp. Ueber das Verhalten des Harnstoffes und des Reststickstoffes im Blute von Nephritikern, *ried Klin*, Berlin, 1913, ix, 912.

nitrogen as an average of 91.2 per cent of the total nonprotein nitrogen. The highest total nonprotein nitrogen he reported was 289 mg per hundred c c of blood in a case of mercury poisoning. Agnew¹⁴ in 1914 reports a series of estimations of total nonprotein nitrogen and urea nitrogen.

The more recent work on the subject of nitrogen partition has been done by Folin and his co-workers. In 1913, Folin and Denis¹⁵ reported on the determination of nitrogenous waste products, and stated that they had found no particular diagnosis to correspond with any particular degree of nitrogen retention. At the same time Seymour¹⁶ reported a series of determinations of total nonprotein nitrogen, urea nitrogen, and uric acid in the blood. In 1914, Folin and Denis¹⁷ reported further on the influence of diet on these same nitrogenous bodies. Again in 1914, Folin and Denis¹⁸ reported a series of twenty-seven estimations of the total nonprotein nitrogen, ammonia nitrogen, uric acid, creatinin, and combined creatinin and creatin, in cases both of health and disease. In four estimations on healthy individuals, the total nonprotein nitrogen varied from 24 to 37 mg per hundred c c of blood, urea nitrogen from 11 to 18 mg, ammonia nitrogen from 0.1 to 0.14 mg, uric acid from 2 to 3 mg, creatinin from 1.1 to 1.3 mg and combined creatinin and creatin from 6.5 to 9.5 mg per hundred c c of blood. In pathologic conditions, figures were found as high as 326 mg for the total nonprotein nitrogen in a case of decompensated cardiorenal disease. In uremia the highest figures found for the various nitrogenous bodies were, total nonprotein nitrogen 264 mg, urea nitrogen 228 mg, ammonia nitrogen 0.66 mg, uric acid 6.6 mg, creatinin 26 mg, and combined creatinin and creatin 46 mg, all per hundred c c of blood. In 1915 Foster¹⁹ reported he had found substantially the same figures in

14 Agnew, J. Howard. Comparative Study of Phenolsulphonephthalein Elimination, and the Incoagulable Nitrogen in the Blood in Cardiorenal Diseases, *THE ARCHIVES INT MED*, 1914, *xiii*, 485.

15 Folin, Otto, and Denis, W. Nitrogenous Waste Products in the Blood in Nephritis, Their Significance and the Methods of Determination, *Medical Communications, Massachusetts Med Soc*, 1913, *xxiv*, 157.

16 Seymour. Nitrogenous Waste Products in the Blood, Their Effect in Chronic Interstitial Nephritis, *Medical Communications, Massachusetts Med Soc*, 1913, *xxiv*, 163.

17 Folin, Otto, Denis, W., and Seymour, Malcolm. The Nonprotein Nitrogenous Constituents of the Blood in Chronic Vascular Nephritis (Arteriosclerosis) as Influenced by the Level of Protein Metabolism, *THE ARCHIVES INT MED*, 1914, *xiii*, 224.

18 Folin, Otto, and Denis, W. On the Creatinin and Creatin Content of Blood, *Jour Biol Chem*, 1914, *xvii*, 487.

19 Foster, Nellis B. Uremia. The Nonprotein Nitrogen of Blood, *THE ARCHIVES INT MED*, 1915, *xi*, 356.

nitrogen partition as had Folin. In addition, four estimations of the amino-acid nitrogen gave values between 4 and 6 mg per hundred c c of blood.

Nitrogen studies in the spinal fluid have been confined largely to estimations of the urea content. The literature was reviewed in 1909 by Mollard and Froment,²⁰ and brought up to date in 1914 by Soper and Granat.²¹ Figures given by various investigators for the normal urea content vary from 0 to 40 mg per hundred c c of spinal fluid, but practically all authors agree that it is greatly increased in uremia. Mestrezat²² in 1912 gives the normal urea content as 6 mg and the total nonprotein nitrogen as 16.7 mg per hundred c c of spinal fluid. Galletta²³ in 1908 gave the total nonprotein content as 20.6 mg, and Comba²⁴ in 1899, as 15 mg per hundred c c of spinal fluid. Both authors cite cases of uremia in which the nonprotein nitrogen retention is vastly increased. Widal²⁵ and Javal²⁶ in 1911 showed that the concentration of urea in the various body fluids is substantially the same. Soper and Granat²¹ in 1914 reported a series of urea estimations in the spinal fluid, using the hypodermic methods, and emphasized the prognostic significance of these. Moral and Froment²⁷ in 1913 reported a case of amyloid kidney, in which they found a total nonprotein nitrogen retention of 222 mg, per hundred c c of spinal fluid, of which 220 mg were represented as urea nitrogen.

In my series of cases, about 175 c c of blood were received directly from the vein into a cylinder containing 3 c c of a 20 per cent solution of potassium oxalate. The cylinder was rapidly shaken to prevent clotting. Lumbar puncture was done immediately thereafter, and about 10 c c of spinal fluid withdrawn.

20 Mollard and Froment. Uree dans le liquide cephalo-rachidien et uremie nerveuse, *Journal de Physiol et de Path. Général*, 1909, **VI**, 263.

21 Soper, Willard B, and Granat, Selma. The Urea Content of the Spinal Fluid with Special Reference to Its Diagnostic and Prognostic Significance, *THE ARCHIVES INT MED*, 1914, **XXII**, 131.

22 Mestrezat. *Le Liquide Cephalo-Rachidien*, Paris, 1912.

23 Galletta. Quoted by Mestrezat, Note 22.

24 Comba. Quoted by Mestrezat, Note 22.

25 Widal. Le pronostic dans le mal le Bright par le dosage de l'urée du sang. Les remissions temporaires et trompeuses de l'azotémie, *Soc med d hôp de Paris*, 1911, **XXVII**, 627.

26 Javal. La grande azotémie. Ses formes, son évolution, son pronostic étudiés par le dosage méthodique de l'urée dans le sang et dans les sérosités de l'organisme, *Soc med d hôp de Paris*, 1911, **XXVII**, 485.

27 Moral and Froment. A propos d'un cas de néphrite amyloïde, rétention de l'urée dans le liquide cephalo-rachidien, *Lyon med*, 1913, **CXX**, 933.

In all estimations on the blood, whole blood was used. Total non-protein nitrogen,²⁸ ammonia nitrogen,²⁸ creatinin,²⁹ and combined creatin and creatinin²⁹ were done by the methods of Folin and Denis. Uric acid was determined by the method of Folin and Denis,³⁰ using the later modification of Folin and Bell,³¹ in which sodium thiocyanate is used in place of hydrogen sulphid. Urea nitrogen was determined by the method of Van Slyke,³² using the colorimeter. The amino-acid nitrogen was estimated with Van Slyke's micro-apparatus.³³ Chlorids were estimated by the method of McLean.³⁴ Total nonprotein nitrogen and urea nitrogen determinations in the spinal fluid were done synchronously with the determinations in the blood. All results were controlled and were repeated when the difference between the estimations was appreciable. The systolic and diastolic blood pressures were taken just before bleeding, and phenolsulphonephthalein tests were done in all instances. The creatin was estimated as the difference between the combined creatinin and creatin determination, and the creatinin determination. The uric acid, creatinin, and creatin nitrogen were figured from the structural formula of each, and are reported as mg per hundred c c.

The cases are reported in three groups: (1) those cases which presented no retinal changes whatsoever, (2) those cases which presented the retinal picture of arteriosclerosis, with occasional hemorrhages, but without exudates, (3) those cases which showed a marked albuminuric retinitis, with haziness or obliteration of the disk outlines, vascular changes, hemorrhages and exudates, with involvement of the macula region.

While the highest retention observed, 266 and 257 mg of nonprotein nitrogen per hundred c c of blood, happened to occur in cases of albuminuric retinitis, nevertheless marked retinitis occurred at practically any level of nitrogen retention. There appears to be no close relationship whatsoever between either total nonprotein nitrogen retention, or any component part, and the occurrence of albuminuric retinitis. A comparison of the three groups fails to show any appreciable

28 Folin, O, and Denis, W. New Methods for the Determination of Total Nonprotein Nitrogen, Urea and Ammonia in the Blood, *Jour Biol Chem*, 1912, xi, 527.

29 Folin, O, and Denis, W. On the Determination of Creatinin and Creatin in Blood, Milk and Tissues, *Jour Biol Chem*, 1914, xvii, 475.

30 Folin, O, and Denis, W. A New (Colorimetric) Method for the Determination of Uric Acid in Blood, *Jour Biol Chem*, 1912-1913, xii, 469.

31 Courtesy of Drs Folin and Bell. Method as yet unpublished.

32 Van Slyke and Cullen. A Permanent Preparation of Urease and Its Use in the Determination of Urea, *Jour Biol Chem*, 1914, xix, 221.

33 Van Slyke and Meyer. The Amino-Acid Nitrogen of the Blood, *Jour Biol Chem*, 1912, xii, 399.

34 Courtesy of Dr McLean. As yet unpublished.

difference in the proportions of either urea, ammonia, uric acid, creatinin, creatin, or amino-acid nitrogen. The same proportions prevail in cases in which there is albuminuric retinitis and those in which the fundi are normal. Neither to urea nor to "any closely allied nitrogenous body" can albuminuric retinitis be attributed. This holds true for the cerebrospinal fluid, also, so far as nitrogen retention could be studied. The three groups show essentially the same picture. Case 13 was of especial interest in that the patient presented a fresh albuminuric retinitis together with a normal nitrogen content throughout. He was a man of 52 years, admitted in apoplectic coma, with a systolic blood pressure of 285 mm Hg, marked retinitis and a phenol-sulphonephthalein output of 28 per cent. He made a good recovery and was discharged from the hospital in fair condition.

An analysis of the figures shows that the urea maintains roughly the same concentration as the total nonprotein nitrogen rises, an average throughout of 63.4 per cent of the total nonprotein nitrogen. While the ammonia nitrogen increased slightly as the total nonprotein nitrogen rose, this rise was not proportional. The relation of ammonia nitrogen to total nonprotein nitrogen accordingly varied from about 0.4 per cent at the low levels of total nonprotein nitrogen to about 0.1 per cent at the highest levels. The uric acid figures were the last to show any marked increase as the total nonprotein nitrogen rose. But two cases showed any marked uric acid retention—Nos. 9 and 17B, in which the uric acid content was respectively 5 and 8.35 mg per hundred c c of blood. In these two cases blood was taken 36 and 12 hours before death. The creatinin showed roughly a proportionate increase as the total nonprotein nitrogen rose, averaging in all 3.4 per cent of the total nonprotein nitrogen. The creatin percentage, excluding Case 18, varied from about 2 per cent to 7 per cent throughout, averaging 3.9 per cent. In Case 18 it reached the high value of 12 per cent. The amino-acid nitrogen, however, showed no constant increase as the total nonprotein nitrogen rose to higher levels, remaining generally between 4 and 7 mg per hundred c c of blood. In Cases 9, 10, 15B and 16A it reached higher levels, but in each of these cases there was an extraneous factor. Case 9 was one of complete anuria for seven days, the blood being taken on the fifth day, while in Cases 10, 15B and 16A the blood was taken about one hour after the midday meal. In all other cases blood was taken four hours after the midday meal.

In the limited number of cases in which as complete partitions as possible were done, figures are given showing the "residual nitrogen." These figures were obtained by subtracting the sum total of the determined component nitrogen constituents from the total nonprotein

nitrogen It includes, therefore, the total error of all the various estimations, and such other unknown nitrogenous bodies as may enter the blood stream These figures are of interest in that they seem in several cases to run roughly parallel with the severity of the case as observed clinically In Case 9, in which the high figure for "residual nitrogen" of 31.55 mg per hundred c c of blood was reached, after five days of complete anuria, death occurred in thirty-six hours In Cases 7, 8 and 16, in which the values were all over 10 mg per hundred c c of blood, death occurred in two days, one month and two months respectively In Cases 11 and 12 with high figures for residual nitrogen, the prognosis from the clinical standpoint seemed extremely poor In the remaining cases in which residual nitrogen was estimated, the patients were all in reasonably fair condition

The total nonprotein nitrogen in the spinal fluid was, as a rule, about 25 per cent lower than that in the blood In two cases, however, the total nonprotein nitrogen was the same in both The first of these (No 8) was one of mercurial poisoning, with practically complete anuria for five days previous to death Blood and spinal fluid were taken eighteen hours before exitus The figures here are comparatively low when compared to Philipp's case of mercurial poisoning, which showed a nonprotein nitrogen retention of 289 mg The second of these two cases was one of seven days' complete anuria and the blood and spinal fluid were taken on the fifth day It seems possible that certain nitrogenous bodies, normally not present in the spinal fluid, are, in anuria, excreted from the blood into the spinal fluid until an equilibrium is reached Sufficient spinal fluid was never obtained in any case to determine if these bodies were any of the common nitrogenous constituents of the blood, for example, uric acid, creatinin, creatin or amino-acids The urea content of the spinal fluid throughout approximately equaled that of the blood, as shown before by Widal, Javal and others It does not seem probable that nitrogen determinations in the spinal fluid give any greater diagnostic or prognostic significance than those in the blood

The concentration of urea in the spinal fluid, in relationship to the total nonprotein nitrogen, was fairly constant throughout, averaging approximately the same percentage at high as at low levels, an average of 78 per cent in the series as a whole

The chlorids in the blood showed little variation, varying in most cases between 0.42 and 0.53 gm per hundred c c In the case of mercury poisoning the low figure 0.34 gm per hundred c c was reached Isolated determinations of blood chlorids without taking into consideration the relative intake and excretion, give little or no information about salt retention

TABLE I—CHRONIC NEPHRITIS WITH NORMAL FUNDI

No	Hosp Med No.	Blood Nitrogen									Spinal Fluid Nitrogen		Blood Pressure	Phthalein Excretion Percentage in 2 Hrs	Remarks
		Total Non- protein	Urea	Am- monia	Uric Acid	Oreat- Inlin	Oreat- tin	Amino Acid	"Resid- ual"	Ohlo- rids, Gm	Total Non- protein	Urea			
1	2,323	26.77	14.33	0.09	0.40	0.77	0.99	6.78	3.36	0.4470	17.85	11.09	130 85	48	Normal control
2	2,319	29.43	15.63	0.15	0.31	0.57	0.65	5.42	6.67	0.4135	21.68	15.45	240 160	47	
3	2,357	37.70	18.49	0.10	0.67	0.67	0.95	8.41	6.48	0.4391	27.35	18.50	210 108	52	Chr myocarditis
4	2,348	43.48	23.57	0.12	0.40	0.59	1.19	6.52	11.09	0.4707	35.70	21.25	185 95	52	
5	1,992	55.30	38.93	0.11	0.67	3.07	4.27			0.5153			260 110	12	
6	1,954	57.60	30.85	0.15	0.64	0.82	5.70			0.4296			235-115	21	Mercury poisoning
7A†	2,000	{ 95.27 60.66	{ 62.50 95.10	0.19	0.53	5.08	2.32	6.42	13.86	0.5082	66.66	60.24	190 98	Unreadable trace	
7B;†															
8	2,229	123.00	65.10	0.16	0.68	5.29	7.08	5.89	13.80	0.3129	128.00	95.21	130 80	Unreadable trace	
9	2,171	138.10	79.70	0.24	1.67	4.69	4.37	16.32	31.56	0.4216	142.96	85.88	185-140	Unreadable trace*	

* Phthalein estimation made three weeks previously at Massachusetts General Hospital † 7A on December 12 † 7B on December 17

TABLE 2—CHRONIC NEPHRITIS WITH VASCULAR CHANGES ONLY IN FUNDI

No	Hosp Med No	Blood Nitrogen							Spinal Fluid Nitrogen		Blood Pressure	Phthalein Excretion Percentage in 2 Hrs	Remarks
		Total Non protein	Urea	Ammonia	Uric Acid	Creatinin	Creatinin	Amino Acid	"Residual"	Chlorids, Gm	Total Non protein	Urea	
10	2,132	47.51	29.53	0.18	0.40	2.02	3.58	10.23	1.52	0.4500		33	265/140
11	2,202	71.34	43.07	0.11	0.66	1.71	2.10	6.50	17.28	0.5362	47.62	40.32	245/150
12	2,316	95.23	60.00	0.16	0.43	3.63	4.34	8.05	18.57	0.4649	80.00	60.16	213/124
												Unreadable trace	17 cells in sp fl

TABLE 3—CHRONIC NEPHRITIS WITH MARKED ALBUMINURIC RETINITIS

No	Hosp Med No	Blood Nitrogen							Spinal Fluid Nitrogen		Blood Pressure	Phthalein Excretion Percentage in 2 Hrs	Remarks
		Total Non protein	Urea	Ammonia	Uric Acid	Creatinin	Creatinin	Amino Acid	"Residual"	Chlorids, Gm	Total Non protein	Urea	
13	2,354	23.81	14.60	0.10	0.35	0.61	0.99	4.02	3.14	0.4243	20.00	12.50	285/160
14	2,074	40.98	27.00	0.17	0.39	1.67	2.21	5.22	4.32	0.4400	33.23	26.32	180/130
15A†	2,043	{ 54.05	32.14	0.12	0.46	2.74	2.74			0.4558	43.46	26.59	250/166
15B†		{ 60.61	41.54	0.12	1.26	2.30	3.12	10.64	1.63	0.4735	46.53	31.25	250/160
16A	2,108	{ 65.55	29.35	0.09	0.60	2.63	1.59	9.44	11.85	0.4407	37.21	27.77	190/150
16B		{ 47.54	25.50	0.15	0.98	2.45	3.66	6.56	8.24	0.3997	33.33	26.00	150/130
17A#	1,882	{ 192.30	113.80	0.20	0.62	8.01	14.39		0.4783	0.5141	125.00	111.11	248/128
17B§		{ 266.66	166.45	0.21	2.73	7.85	7.66		0.4752		183.69	166.66	250/130
18	1,975	257.70	181.80	0.33	1.51	6.01	30.93					Unreadable trace	208/152
												Unreadable trace	Four cells per cm in spinal fluid
												Unreadable trace	Herpes zoster complicating uremia
												Unreadable trace	Ninety one cells
												Unreadable trace	Sixteen cells per cm spinal fluid
												Unreadable trace	Uremia Twenty three cells per cm in spinal fluid
												Unreadable trace	Uremia

† 15A on December 19 ‡ 15B on December 30 || 16A on January 4 ¶ 16B on January 19 # 17A on November 30 § 17B on December 14

The relationship between nonprotein nitrogen retention and phenol-sulphonephthalein excretion was fairly constant. When the nitrogen retention was high, the phenolsulphonephthalein excretion was generally low, and vice versa, confirming the results of the numerous investigators in this field. No relationship between the nonprotein nitrogen retention and blood pressure was observed.

CONCLUSIONS

1 There is no apparent relationship between the retention of any nitrogenous body and the occurrence of albuminuric retinitis, and there is certainly no evidence that they stand in the relationship of cause and effect.

2 In the limited number of cases in the series, there seemed to be a more than casual relationship between the "residual nitrogen" of the blood, and the severity of the case as observed clinically.

3 As the level of nonprotein nitrogen rises, the component nitrogenous bodies increase, and in the case of the chief constituents, this rise is proportioned.

4 Estimations of total nonprotein nitrogen and of urea in the spinal fluid give no greater diagnostic or prognostic significance than estimations of these substances in the blood.

5 The variations in chlorid concentration in the blood are so small that in themselves they give no idea of salt retention.

I wish to express my thanks to Dr. Henry A. Christian for his advice and for facilities placed at my disposal during the course of this work, and to Dr. Francis W. Peabody for many helpful suggestions.

A STUDY OF THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF VENOUS PRESSURE OBSERVATIONS IN CARDIAC DISEASE *

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That high venous pressures occur in cases of cardiac decompensation has been observed by Gaertner,¹ Moritz² and von Tabora,³ Frank and Reh,⁴ Sewall,⁵ Schott,⁶ Hooker and Eyster,⁷ and others. The routine measurement of venous pressure at frequent intervals as a means of following the stages of compensation or decompensation, however, has received little attention. The following investigation was undertaken with the purpose of ascertaining whether there is any diagnostic or prognostic significance in repeated venous pressure observations on cardiac cases.

METHOD

A number of instruments and methods have been devised by various workers to measure venous pressure. The technic and relative value of the methods used until 1914 have been summarized by Austin.⁸ Of these, the direct method of Moritz and von Tabora of introducing a hollow needle directly into the vein, while perhaps giving a greater refinement of accuracy, would manifestly be open to serious objections in cases in which a large number of readings were made at frequent intervals. Probably the most useful clinical method was devised by Hooker⁹ in 1914, and it is his instrument which has been used in this investigation. As shown in Figure 1, it consists essentially of a small glass cup (*B*) 2 cm. in diameter and 1 cm. deep, connected with a water manometer. The chamber is sealed to the skin over a suitable vein on the back of the hand by a rim of collodion. In drying, the collodion draws the skin slightly inward, so removing possible error due to superficial tissue tension. The manometer is connected

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* From the Medical Clinic of the Johns Hopkins Hospital

1 Gaertner *Munchen med Wchnschr*, 1903, 1, 2038

2 Moritz and Von Tabora *Deutsch Arch f klin Med*, 1910, xcvi, 475

3 Von Tabora *Munchen med Wchnschr*, 1910, lvi, 1265

4 Frank and Reh *Ztschr f exper Path u Therap*, 1912, x, 241, 1913, xiii, 37

5 Sewall *Jour Am Med Assn*, 1906, xlvii, 1279

6 Schott *Deutsch Arch f klin Med*, 1912, cviii, 537

7 Hooker and Eyster *Johns Hopkins Hosp Bull*, xix, 274

8 Austin *Blood Pressure Its Clinical Application*, G W Norris, 1914, 129

9 Hooker *Am Jour Physiol*, 1914, xxxv, 73

to the cup by a rubber tube, and by compressing the manometer bulb (C) the air pressure in the cup is increased. If the vein be observed by oblique illumination the point at which it definitely begins to collapse can be read in centimeters of water on the manometer scale. Hooker finds that "the most consistent results are obtained when the reading is made at the point where slight oscillations of pressure cause the vein shadow to come and go promptly just before the vessel is completely collapsed." This point has been used throughout this investigation. In all readings the same section of vein was constantly observed.

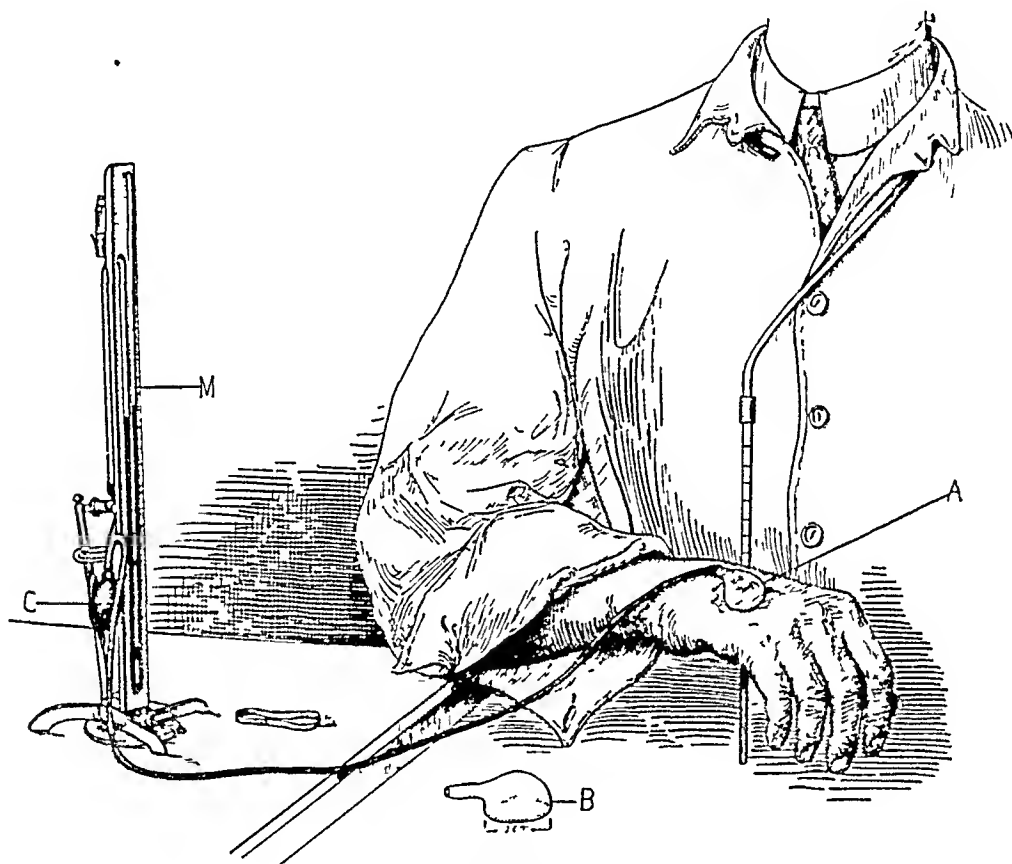


Fig 1—Hooker's venous pressure apparatus. A small glass chamber (B) measuring 1 by 2 cm. is held temporarily by a rubber band over a suitable vein on the back of the hand, as shown at (A). A rim of collodion is applied and in drying it seals the chamber to the skin. The rubber band is then removed and the chamber connected by a rubber tube to the water manometer (M). By pressing on the manometer bulb (C) the air pressure in the chamber is raised and a reading is made "at the point where slight oscillations of pressure cause the vein shadow to come and go promptly just before the vessel is completely collapsed." This pressure is recorded directly by the water manometer. The hand is held at the level of the mid point of the anterior-posterior diameter of the body at the costal angle.

As to the so-called "heart level," an arbitrary level in relation to the heart which must be chosen in order to give a constant point for making readings, the level originally defined by von Recklinghausen

and subsequently adopted by Hooker, has been used. This was chosen as the midpoint of the anterior-posterior diameter of the body at the costal angle. The hand, in each observation in this series, was placed on a pillow or other support at this level and was maintained quietly for at least three minutes to allow the hydrostatic factors to become adjusted and constant. As most patients with cardiac decompensation lie in bed with the body at an angle of about 45 degrees to the horizontal, this position was also adopted as the position in which to make the readings. In those cases with a venous pressure higher than the manometer could record, the hand was raised above the "heart level" until the venous pressure was within the range of the manometer. This hydrostatic column in centimeters was then added to the venous pressure.

It was further necessary to adopt the following three conditions. First, the vein must stand out sufficiently from the surrounding skin level to give a distinct shadow by oblique illumination. Second, the vein wall must be collapsible. Third, the patient must be lying quietly and undisturbed in bed.

Obviously not every cardiac case could be studied. Old patients with phleboscrosis, patients with exceedingly edematous or fat hands, and patients with continuously small veins, had to be passed by. Nevertheless, excluding the rare cases of patients with hardened vessels there were few cases that did not show satisfactory veins on the back of the hand at some time during the day.

MATERIAL

Two hundred and seventy-six venous pressure observations have been made on fourteen cases at various stages of cardiac decompensation. The largest number of readings on a single case was seventy-three (Case 1), covering a period from November 5 to March 7. The lowest number was five (Case 14). In addition to the venous pressure, the systolic and diastolic arterial pressures by the auscultatory method, the pulse rate, the treatment, and the clinical condition of the patient were noted. The fluid intake and output for each twenty-four-hour period was recorded in the majority of cases. At each observation the venous pressure was taken before any of the other data in order to disturb the patient as little as possible. The highest venous pressure recorded was 50 cm. of water (Case 2) which exceeds any record found in the literature. This reading was made by two observers. A case was followed only so long as the venous pressure remained high or there was any doubt as to compensation. Five (Cases 2-6) of the fourteen patients died. In addition to these fourteen cases, eight cases were studied to determine the diurnal variation in venous pressure.

Before giving the results which were found, it would be well to state the factors which alter venous pressure, as observed by previous workers, especially in their relation to the present investigation. Barach and Marks¹⁰ in a series of forty-eight normal cases noted a fall in venous pressure on passively changing from the erect to the horizontal position, and a rise of pressure in returning to the erect posture. Hooker,¹¹ Elpers,¹² and Schott⁶ found that muscular exertion

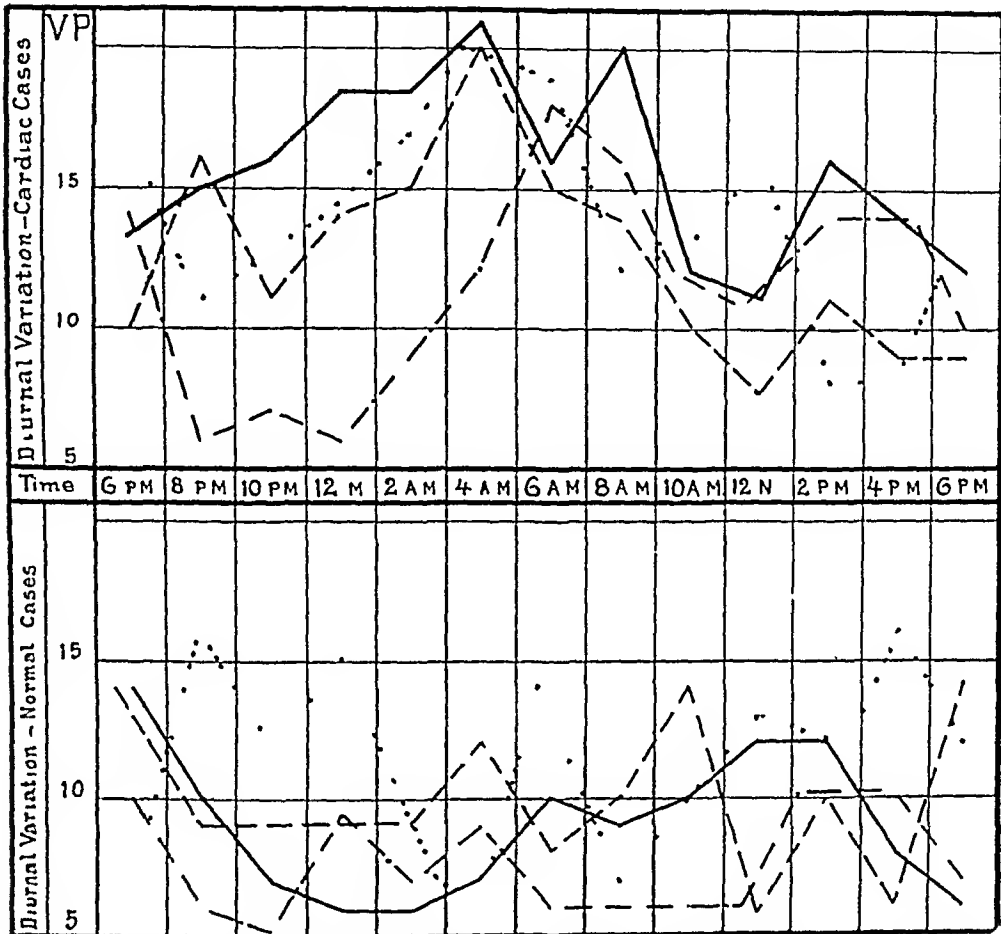


Fig 2—Curves showing the diurnal variation in four cardiac and four normal cases. The patients were all in bed under similar ward conditions. Note that in the cardiac cases the highest venous pressures occur at night, while in the normal cases there is an almost complete reversal of the picture, the lowest venous pressures tending to occur during the sleeping hours.

increases the venous pressure. The work of Elpers¹² would indicate that heat and cold increase the venous pressure, and finally, Hooker⁹ has demonstrated a distinct diurnal variation in the venous pressure.

Obviously, for a patient lying quietly in bed under the conditions which were observed, the factors of temperature change, of muscular

10 Barach and Marks. *THE ARCHIVES INT MED* 1913, VI, 485

11 Hooker. *Am Jour Physiol* 1911 XXVIII, 235

12 Elpers. *Innere Diss*, Kiel, 1911

exertion, and of posture were practically constant Under ideal experimental conditions these factors could hardly have been more carefully regulated As to the complete diurnal variation under these conditions no data could be found, although Hooker⁹ noted a distinct diurnal variation under normal conditions of health and a decided fluctuation in venous pressure during the day in three surgical cases confined to bed

DIURNAL VARIATION

In view of these observations by Hooker, it was necessary, before it could be decided what constitutes a pathological venous pressure, to see what part the diurnal variation plays in the determinations made on patients confined to bed To answer this question eight patients were selected on the medical wards Only those cases which showed

TABLE 1—CARDIAC CASES

Case	Max V P		Min V P		Diurnal Variation Cm H ₂ O
	Reading	Time	Reading	Time	
S	21	4 a m	11	12 noon	10
T	20	4 a m	8	12 noon	12
M	20	4 a m	8	2-4 p m	12
J	18	6 a m	6	8-12 p m	12

TABLE 2—NORMAL CASES

Case	Max V P		Min V P		Diurnal Variation
	Reading	Time	Reading	Time	
D	14	6 p m	6	12 a m	8
G	14	6 p m	6	4 a m	8
W	10	6 p m	8	12-4 p m	10
L	16	2 p m	5	6 a m	9
.		8 p m	6	10 p m	
				4 a m	

excellent veins for reading were chosen Four of these cases were at various stages of cardiac decompensation, and four had no cardiac complications The observations were made at two-hourly intervals over a period of twenty-four hours The glass cups were left attached during the entire period so that to make a reading it was only necessary to connect the manometer tube All the patients were in the same ward environment under constant and similar conditions, and during

the twenty-four-hour period they remained in bed. There was a difference, however, between the cardiac and normal cases during the night, in that the normal patients lay flat in bed while the cardiac patients remained propped in a semi-erect posture. During the night it was possible to make the majority of readings without waking the patients, a small pocket electric light being used.

The eight cases are plotted in the curves shown in Figure 2. It is evident from these curves that there is a definite diurnal variation in venous pressure even under the constant conditions of the experiment. In comparing the curves of the normal and cardiac cases certain differences can be seen which are tabulated in Tables 1 and 2.

The first and striking fact is that in the cardiac cases the highest venous pressures occur in the early morning hours, while in the normal cases, as Hooker⁹ found, the lowest venous pressures tend to occur at night. The second fact is that the diurnal variation averages 2.5 cm. more in the cardiac than in the normal cases. This greater change of pressure is interesting in connection with the observations of Schott,⁶ that venous pressure can be altered by exercise in proportion to the degree of cardiac decompensation.

WHAT SHOULD BE CONSIDERED AS A PATHOLOGICAL VENOUS PRESSURE?

Since, therefore, a daily variation of from 8 to 12 cm. in venous pressure has been found in ward cases, the essential question is, what can be regarded as a pathological venous pressure? It is generally admitted that venous pressure observed at a fixed point and level is a fair indication of the feeding pressure of the heart. What, however, is the border-line between an efficient feeding pressure and a pressure due to an incompetent heart that cannot handle the blood with which it is supplied? With the factor of diurnal variation to be considered, an observation made one day might give the lowest and a reading the following day the highest pressure of a normal diurnal variation, and so one might be led to believe that there had been an abnormal increase in the venous pressure.

Various observers, depending on the method used, have given different values as to the upper limits of a normal pressure. Hooker,⁹ by the method here used, gives 20 cm. as the upper limit of the normal diurnal variation under the varying conditions of daily life. To decide this point, the fourteen cases observed in this series have been classified according to the clinical divisions of "compensated or compensating" and "decompensated or decompensating." These divisions were evident from the clinical signs and symptoms. Of the six patients whose cases were classified as "decompensated," five died, and the sixth

(Case 1) recovered, though it was doubtful for three months whether he would live. At the time of writing none of the "compensated" cases have terminated fatally. All the patients have recovered or are on the way to recovery.

From Table 3 it will be seen that of 171 observations on six "decompensating" cases the average venous pressure in each case never went below 20 cm. while of 105 readings on "compensating" cases, the average of no case ever went above 20 cm. In this number of observations the factor of diurnal variation must be well equalized, for the readings were made at all hours of the day. The average venous pressure for all the "compensating" cases was about 14 cm. and of the "decompensating" cases 26 cm. It would seem, therefore, from these figures, that by this method, a venous pressure above 20 cm. is pathological, while any pressure below this may be regarded as within the limits of normal variation.

TABLE 3—COMPENSATED AND DECOMPENSATED CASES

Case No	Clinical Condition	No Days Observed	Average Venous Pressure, Cm. Water
1	Decompensated	73	28.0 { first, 29 days 20.0 { last, 44 days
2	Decompensated Died	33	29.7
3	Decompensated Died	21	21.0
4	Decompensated Died	8	23.2
5	Decompensated Died	19	29.0
6	Decompensated Died	17	29.3
		T'l 171	Avg 26.0
7	Compensated	8	13.0
8	Compensated	30	10.7
9	Compensated	8	17.4
10	Compensated	25	14.0
11	Compensated	5	10.4
12	Compensating	9	15.2
13	Compensating	15	13.8
14	Compensated	5	19.0
		T'l 105	Avg 14.3

It must be borne in mind, however, that a venous pressure below 20 cm., though indicating that a heart is handling the blood with which it is supplied, nevertheless, does not indicate how narrow the margin is between compensation and decompensation. Thus a heart barely compensating under perfect bodily quiet might give the same venous pressure as a well-compensated heart. Any unusual strain in the former case, however, would be sufficient to throw the heart back into decompensation, while in the latter case decompensation would not occur. It is on this consideration that Schott⁶ based his venous pres-

sure test for the functional capacity of the heart. As shown above, however, the line of immediate danger seems to be at 20 cm. A pressure persisting above this gives a serious, and a pressure below a favorable, outlook.

CLASSIFICATION OF DATA

The deductions which follow are based on the observations stated under "Material" and are illustrated by the curves (Figs 3-6) which demonstrate the most typical findings in the fourteen cases studied. The clinically interesting facts which they illustrate, follow:

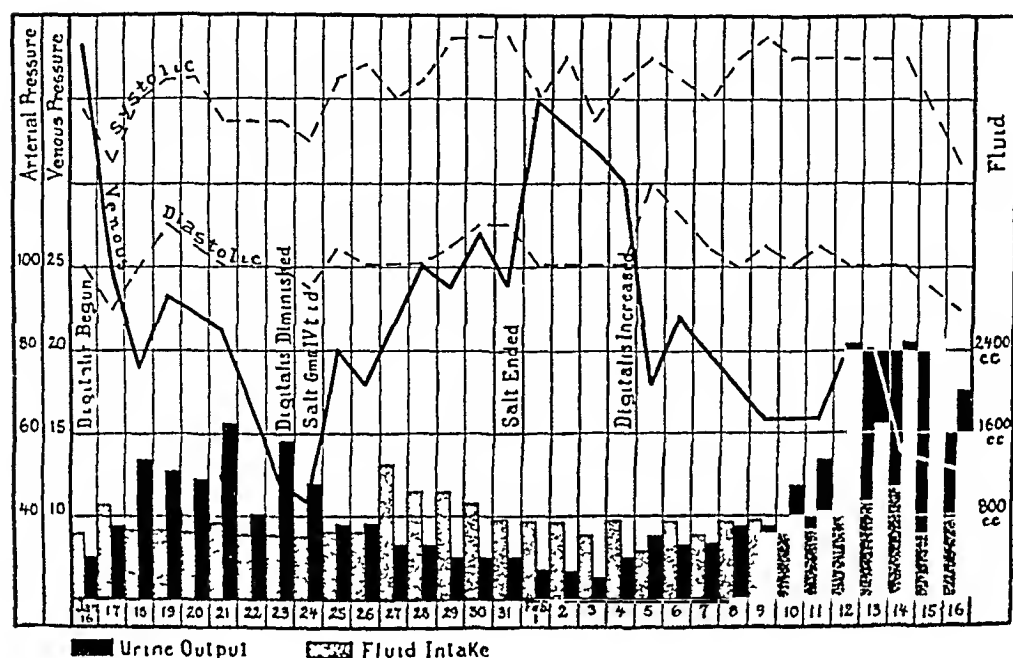


Fig 3—From the chart of Case 1, showing the relation of venous pressure, arterial pressure, fluid intake, and urine output. During the first fall in venous pressure the response in urine output is practically coincident, while after the second drop in pressure there is a delayed response of several days. Note also that the venous pressure gives an indication of the effect of therapy and compensation which are shown in no way by the arterial pressure.

Relation of Venous Pressure to Decompensation—Of the seven cases which showed decompensation (Cases 1-8) all gave a direct relation between venous pressure as followed at frequent intervals and the degree of compensation as indicated by the clinical signs. A pressure continuously above 20 cm almost invariably gave symptoms which called for treatment.

Rise in Venous Pressure Preceding a Break in Compensation—In Case 1 (see Figs 3 and 4) (November 12 to 18, November 23 to 30, December 3 to 11, January 12 to 18, January 26 to February 6), Case 2 (October 15 to 19, November 3 to 8, November 13 to 18, November 23 to 29), Case 3 (see Fig 5) (November 25 to 27, December 7 to 9, December 12 to 20), Case 4 (see Fig 6), Case 5 (October 16 to 26,

October 27 to November 9), and Case 6 (October 16 to November 7, November 10 to 19) a steady rise in venous pressure definitely preceded a break in compensation. When the venous pressure reached a high point the usual clinical signs of decompensation generally became apparent enough to call for treatment. If such treatment had been instituted before the venous pressure had risen to such a height the break in compensation might have been averted and the heart spared.

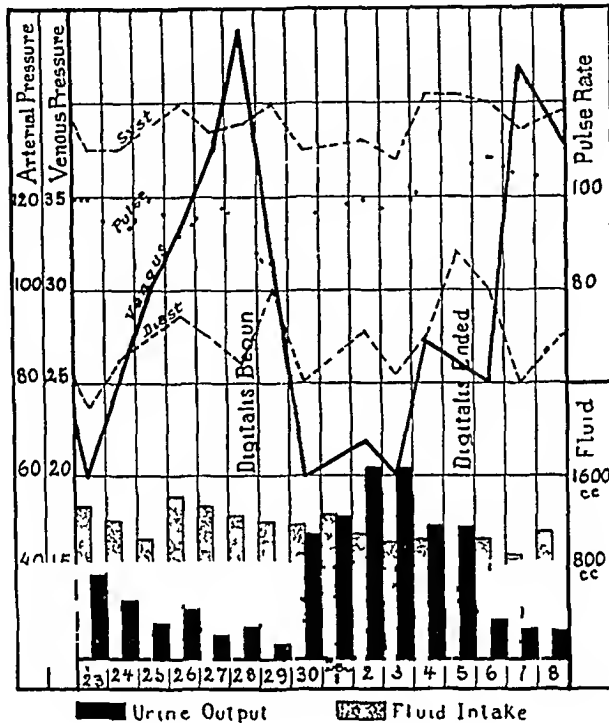


Fig 4—From the chart of Case 1, showing the relation of venous pressure, arterial pressure, and fluid intake and output. A rise in venous pressure and a fall in urine output preceded the clinical signs of decompensation which called for digitalis therapy. Note that neither the systolic nor the diastolic arterial pressures gave any indication of the degree of compensation. Only after the venous pressure had reached a high point did the clinical signs and symptoms become apparent enough to call for treatment.

Relation of Digitalis and Strophanthin to Venous Pressure—All the patients in this series received digitalis or strophanthin either once or oftener during their stay in the hospital. Table 4 groups the results which were found.

TABLE 4—RESULTS OF USE OF DIGITALIS SERIES

Venous Pressure	Died	Compensating *	Decompensating
Definitely lowered by digitalis series	2,	10	1, 7
Not definitely lowered by digitalis series	3, 4 5, 7	8, 9, 11, 12, 13, 14	

* Average venous pressure, 14

This table indicates that of the five cases which terminated fatally (See Figs 5 and 6 as examples) only one showed lowering of the venous pressure as a result of cardiac tonics, while of the "compensated" cases also, only one showed a lowering of the venous pressure. In this latter case the variation was in the limits of normal. The lack of effect of digitalis or strophanthin on compensated cases would seem to be in accord with the experimental evidence of Capps and Mathews,¹³ that the digitalis group does not materially alter the venous pressure in normal animals. The two decompensating cases in which the patients did not die gave a striking response to the digitalis group (See Figs 3, 4, and 6)

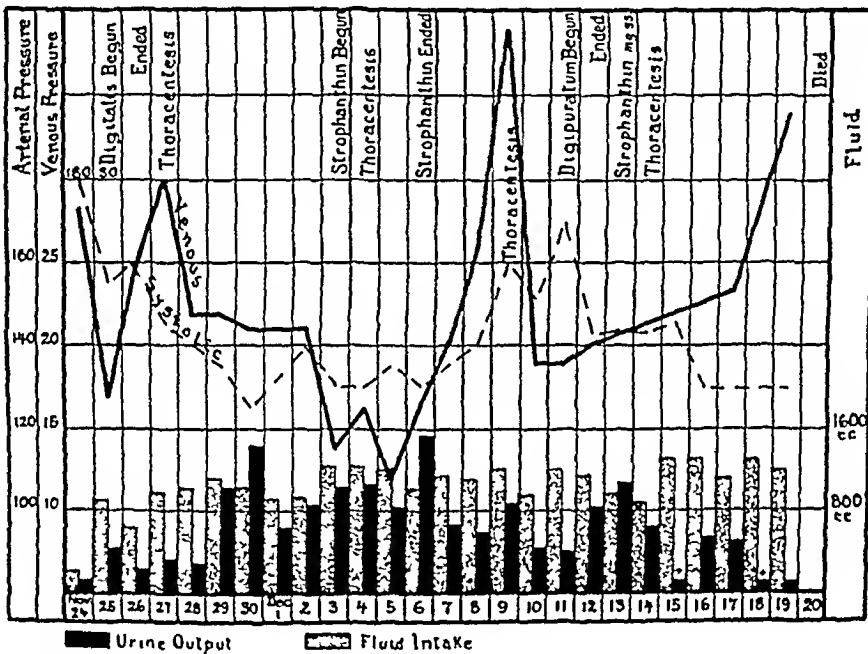


Fig 5—Case 3 Chart showing the relation of venous pressure, systolic arterial pressure, and fluid intake and output from admission to the hospital until death. The diastolic pressure could not be determined because of the extreme degree of aortic insufficiency. Note that from December 8 to 12 there was a coincident rise of venous and arterial pressures, but that before death the arterial pressure fell as the venous pressure rose.

If any conclusions can be drawn they would seem to be, first, that with the venous pressure continuously below 20 cm the effect of digitalis cannot be followed by the venous pressure, and second, a venous pressure continuously above 20 cm, which is not lowered by digitalis, is an indication of grave cardiac involvement.

High Venous Pressure Before Death—Of the five patients who died (2, 3, 4, 5, 6) all gave high venous pressure readings before death. Case 4 gave a reading of 38 cm six hours before, while Case 3

¹³ Capps and Mathews. Jour. Am. Med. Assn. 1913, lvi, 388.

showed a pressure of 34 cm fourteen hours before exitus. It was impossible to make readings on Cases 2 and 5 immediately before death, but so long as observations were possible, each showed, over a period of two weeks, average venous pressures of 37 cm and 30 cm respectively. Case 6, a typical cardiorenal, was continuously on the verge of severe decompensation. While under observation the patient's venous pressure averaged 29 cm over a period of five weeks, and he died shortly after leaving the hospital. A rapid rise of venous pressure, however, in all the cases observed, did not invariably end unfavor-

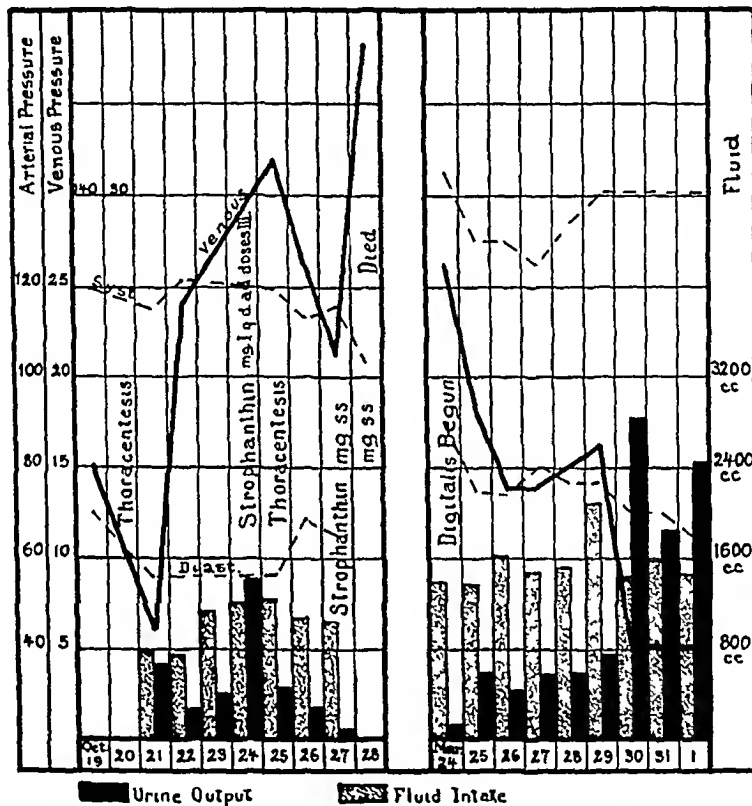


Fig 6—Case 4 (left), Case 7 (right). Charts of two cases of severe myocardial insufficiency, one ending in death, the other in recovery, showing the relation of venous pressure, arterial pressure, and fluid output and intake. Note that in the case which ended fatally the venous pressure steadily rose, the urine output diminished, and the systolic pressure fell with a lowering of the pulse pressure in spite of thoracentesis and strophanthin. In the case which ended in recovery the venous pressure fell rapidly, and the urine output and pulse pressure responded four days later to simple digitalis therapy.

ably, as can be seen by glancing at Figures 3 to 6. The proper therapy often lowered a high venous pressure. The interesting facts nevertheless remain, first, that so long as observations were possible no patient died with a low venous pressure, and second, that a rapid elevation of pressure to a high level, or a continuously high average venous pressure, was of serious prognostic significance.

Relation of Arterial to Venous Pressure—The relation between arterial and venous pressure, as found in these cases, is interesting

Plumier's¹⁴ experiments on animals support the theoretical conclusion that venous and arterial pressure vary inversely Elpers,¹² Schott,⁶ and others, in human cases, have found that the height of venous pressure is not passively dependent on the height of arterial pressure Isolated observations by me on several cases of extreme hypertension in which compensation was perfect, did not give high venous pressure readings One case brought to the accident department with cerebral hemorrhage showed a systolic pressure of 300 mm , a diastolic of 180 mm Hg, and a venous pressure of 20 cm water The relations which were noted between arterial and venous pressure are tabulated in Table 5

TABLE 5—RELATIONS BETWEEN ARTERIAL AND VENOUS PRESSURES

	Venous Pressure Shows No Relation to	Venous Pressure Varies Directly with	Venous Pressure Varies Inversely to
Systolic arterial pressure	1 (at first), 2, 7, 10, 11	3 (at first), 5 (at first), 8, 9, 12	3 (before death), 5 (before death), 4, 6
Diastolic arterial pressure	1, 2, 4, 6, 9, 10, 11	7, 8, 12	
Pulse pressure	1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 14		7, 12
Pulse rate	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 13	12	5

Thus, of 12 cases on which sufficient observations were made, 5 showed no relation between the systolic and the venous pressures, in 3, the venous and systolic pressures varied directly, 2 gave an inverse ratio between the pressures, while in 2 cases the venous and arterial pressure varied directly at first, and before death varied inversely In 4 of the 5 cases which terminated fatally, the inverse ratio was noted, that is, the venous pressure rose and the systolic pressure fell before death

Satisfactory diastolic pressure readings could be made in ten cases Seven indicated no relation between diastolic pressure changes and venous pressure changes, while in three there was a fall in venous pressure with a fall in diastolic pressure From the tables, however, it can be seen that this fall in diastolic pressure in Cases 8 and 12 was synchronous with a fall in systolic pressure but that in Cases 7 and 12 there was an increased pulse pressure due to the fall in diastolic pressure

As to the relation of pulse pressure to venous pressure it was found that in eleven cases no relation was noticeable, while in two

14 Plumier Arch internat de Physiol 1909, viii, 1

(See Fig 6, Case 7 as example) there was a fall in venous pressure with an increased pulse pressure

In this connection it is interesting to note the relation of the so-called "amplitude-frequency product" of v Recklinghausen¹⁵ It was suggested by him that the product of the pulse pressure and pulse rate might be a criterion of the condition of the greater circulation Fellner¹⁶ thought he found a relation between this amplitude-frequency factor, and the venous pressure, in cardiac cases Ten cases in this series could be compared as to this point Of these, six, based on 173 observations, showed no definite relation, while four cases, based on 74 observations, showed only an occasional relation between the venous pressure and the amplitude-frequency product In this series, therefore, neither the pulse pressure nor the product of the pulse pressure and the pulse rate seemed to be associated in any definite way with venous pressure

To summarize the relation between the clinical observations of arterial and venous pressures in this series, it may be said that, except for a fall in systolic and a rise in venous pressure before death in four cases, no constant relation could be found between either the systolic, the diastolic, the pulse pressure, or the amplitude-frequency product on the one hand, and the venous pressure on the other, that in general, the venous pressure gave indications of the variations in compensation which were suggested in no way by the data obtainable from the arterial pressure

Relation of Venous Pressure to Urine Output—Clinically and experimentally it is well known that the function of a normal kidney depends largely on the circulation With congestion and slowing of the blood stream the amount of fluid put out by the kidneys is diminished and with a relief of this congestion the kidney function returns to normal Reference to Figures 3 to 6 shows a distinct relation between the venous pressure and the urinary output In a total of 203 observations on ten cases in which the fluid intake and output were studied, this inverse ratio of venous pressure to urinary secretion was noted in seven (1, 2, 3, 4, 7, 10, 13) and was not found in two cases (8, 12) In six of these eight patients it was not apparent which was the first indication of the changed circulation, while in two instances (Figs 3, and 6, Case 7) the drop in venous pressure preceded the polyuria by several days

We would conclude, therefore, from this series that in the majority of cases the venous pressure and the amount of urine varied inversely and that the variations are coincident This would add further evi-

15 Von Recklinghausen Arch f exper Path u Pharm, 1906, lvi, 1

16 Fellner Deutsch Arch f klin Med, 1907, lxxxviii, 1

dence to show that consecutive changes in venous pressure are an indication of the condition of the circulation and heart

Venous Pressure as Related to Intrathoracic Pressure—Cases 2, 3 and 4 in this series had sufficient hydrothorax to make thoracentesis necessary. Eight pleural tapplings were performed on these three cases. The venous pressure was lowered seven times with an improvement in the clinical condition of the patients. (See Figs 5 and 6 as examples.) The final thoracentesis in Case 3 did not lower the venous pressure and the patient died. The intrathoracic pressure was measured twice with a water manometer in Case 3 and in each instance there was a change from a positive to a negative pressure during thoracentesis. This is in accord with the results of Hooker,⁹ who found that increased intrathoracic pressure causes a rise in venous pressure which cannot be compensated. It also emphasizes the value of thoracentesis as a therapeutic measure in relieving an overstrained heart.

Effect of Venesection on Venous Pressure—Table 6 illustrates this point in three cases observed. Venesection, therefore, seems to lower venous pressure, but the subsequent rise in pressure is rapid. The results of von Tabora agree with these observations.

TABLE 6—EFFECT OF VENESECTION ON VENOUS PRESSURE

Patient	Condition	Amount of Blood Drawn cc	Fall in Venous Pressure cm	Subsequent Effect on V P
S H	Emphysema, pulmonary congestion	500	28-9	Following day V P = 18
P W	Myocardial insufficiency Pulmonary congestion	550	29-14	Following day V P = 28
L M	Normal, transfusion donor	540	18-9	Three hours later V P = 15

SUMMARY

1 The venous pressure has been followed at frequent intervals in fourteen cases of cardiac insufficiency at various stages of decompensation and compensation. Two hundred and seventy-six observations have been made. Hooker's modified method has been used, and the conditions which must be observed in making clinical venous pressure readings by this method have been given.

2 A diurnal variation in venous pressure of from 8 to 12 cm of water was noted in four normal and four cardiac cases, all the patients

being confined to bed This variation was based on two-hourly observations over a period of twenty-four hours It was found that the highest venous pressures occurred during the sleeping hours in the cardiac cases, while in the normal cases, as previously observed by Hooker, the lowest pressures of diurnal variation occurred at night

3 In the patients who died, either a rapid rise in venous pressure or a continuously high pressure above the 20 cm level was observed before death

4 A venous pressure continuously above 20 cm, which was not lowered by the digitalis series, was an indication of grave cardiac involvement

5 A venous pressure continuously below 20 cm gave no definite indication as to the effect of digitalis or strophanthin therapy

6 A fall in systolic arterial pressure and a rise in venous pressure occurred in four cases before death Otherwise no constant relation could be noted either between the systolic, the diastolic, the pulse pressure, or the amplitude-frequency product on the one hand, and the venous pressure on the other

7 Venous pressure and urine output generally showed an inverse variation The variation was usually coincident, but, if coincidence did not occur, the changes in venous pressure tended to precede the changes in kidney function

8 The venous pressure was lowered in seven out of eight pleural tappings

9 Venesection lowered the venous pressure in three cases observed, but the subsequent rise in pressure was rapid

CONCLUSIONS

1 Venous pressure measurements, when made at frequent intervals, give a definite indication of the degree, and changes in the degree of cardiac decompensation

2 A venous pressure of 20 cm, by this method, marks the danger line between compensation and decompensation

3 A rise in venous pressure above 20 cm precedes the clinical signs of decompensation

4 Above the 20 cm level a rising venous pressure has an unfavorable, and a fall in venous pressure a favorable prognostic significance

5 Death from cardiac decompensation is preceded by a continuously high venous pressure, or a rapid rise

6 Venous pressure observations at short intervals give information as to the degree of cardiac decompensation which is not obtainable by observation of the arterial pressure

7 Frequent venous pressure measurements not only have a valuable diagnostic and prognostic significance, but also furnish an important indication for, and check on therapeutic measures

Grateful acknowledgment is made to Dr D R Hooker, who supplied the instrument used, and to the clinical staff of the hospital and others who kindly cooperated in this investigation

PROTOCOLS

CASE 1—J S, aged 48, male, colored Admitted Oct 28, 1914 Clinical diagnosis Aortic insufficiency and myocardial insufficiency Eleven months before admission began having shortness of breath and swelling of the abdomen Was improved by three weeks' stay in the hospital during April, 1914 Symptoms returned a few weeks before last admission Admitted with dyspnea, orthopnea, edema of the legs, ascites, moderate hydrothorax, a large tender liver, greatly enlarged area of cardiac dulness and signs of aortic and mitral regurgitation Under digitalis, purgation, diuretics, and limited fluids the patient wavered between compensation and decompensation for about six weeks, then went on to recovery The venous pressure from November 5 to February 7 varied from 44 to 10 cm The average venous pressure for the first twenty-nine days was 28 cm, and for the last forty-four days 20 cm

CASE 2—33,167 F J, aged 49, female, colored Admitted Oct 12, 1914 Clinical diagnosis Aortic insufficiency and myocardial insufficiency, syphilis Three weeks before admission the patient began having shortness of breath, orthopnea, cough and edema of the ankles and feet Admitted to the hospital with dyspnea, orthopnea, tachycardia, and enlarged area of cardiac dulness, the signs of aortic insufficiency and fluid at the bases of both lungs Under limited fluids, purgation, thoracentesis, diuretics, digitalis and strophanthin the patient wavered between compensation and decompensation for five weeks, but finally no longer responded to treatment and died December 15 Necropsy confirmed the clinical diagnosis The venous pressure from October 15 to December 4, when it could no longer be observed because of the edema of the hands, varied from 9 to 50 cm, with an average pressure of 29.7

CASE 3—33,356 S S, aged 45, female, white Admitted Nov 24, 1914 Clinical diagnosis Aortic insufficiency and myocardial insufficiency, syphilis Five months before admission patient began having paroxysmal attacks of dyspnea, orthopnea, severe epigastric pain and edema of the ankles On admission was dyspneic, orthopneic, with ascites, anasarca, hydrothorax and showed a large area of cardiac dulness and the signs of aortic and relative mitral insufficiency In spite of repeated thoracentesis, limited fluids, purgation, diuretics, digitalis and strophanthin the patient did not improve and died about a month after admission Necropsy confirmed the clinical diagnosis The venous pressure observed from admission until death varied from 12 to 39 cm, with an average pressure of 21 cm

CASE 4—33,172 E W, aged 20, female, white Admitted Oct 13, 1914 Clinical diagnosis Acute and chronic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency At 14 years patient began having palpitation and shortness of breath Ten months before admission became pregnant and as pregnancy advanced, dyspnea and palpitation became progressively worse Following delivery on October 6 the patient became no better and in spite of repeated thoracentesis, limited fluids, purgation, diuretics, strophanthin and digitalis, the patient was not improved and died fifteen days after admission Necropsy confirmed the clinical diagnosis Venous pressure from October 19 until death varied from 15 to 38 cm with one reading of 6 cm immediately after thoracentesis The highest venous pressure of 38 cm occurred six hours before death

CASE 5—33,181 P V, aged 52, white, male, admitted Oct 15, 1914 Clinical diagnosis Aortic and mitral stenosis and insufficiency, myocardial insufficiency About a year before admission began noticing shortness of breath and swelling of the ankles Was compelled to stop work Was improved by five weeks' stay in the hospital in February, 1914, but soon relapsed into his previous condition Admitted with dyspnea, orthopnea, anasarca, ascites, a large and tender liver and spleen, and the signs of aortic and mitral stenosis and insufficiency, and myocardial insufficiency Was not improved by limited fluids, Karell diet, purgation, diuretics, digitalis, or venesection, and died four weeks after admission Necropsy confirmed the clinical diagnosis Venous pressure from October 16 to November 10 varied from 16 to 39 cm, with an average pressure of 29 cm

CASE 6—33,104 W H, aged 52, white, male Admitted Sept 30, 1914 Clinical diagnosis Arteriosclerosis, chronic nephritis, hypertension, myocardial insufficiency For five years had slowly increasing dyspnea, weakness, edema of the ankles and swelling of the abdomen For almost a year had been able to do no work Admitted to the hospital with dyspnea, orthopnea, polypnea, ascites, general anasarca, a much enlarged area of cardiac dulness, a blood pressure of 220, right-sided hydrothorax and albuminuria Phenolsulphonephthalein excretion 15 per cent in two hours Showed no improvement under limited fluids, purgation, diuretics and digitalis Remained in hospital for seven weeks and died shortly after returning home Venous pressure from October 16 to November 23 varied from 20 to 41 cm with an average pressure of 29 cm

CASE 7—33,922 P W R, aged 66, white, male Admitted March 23, 1914 Clinical diagnosis Myocardial insufficiency, auricular fibrillation Dyspnea and palpitation on exertion for the past ten years Symptoms became severe two years ago with swelling of the legs and abdomen Was relieved by treatment but has had frequent recurrences Admitted to the hospital with dyspnea, orthopnea, considerable edema and ascites and enlarged area of cardiac dulness, auricular fibrillation, and an enlarged tender liver Under limited fluids, purgation and digitalis he improved rapidly and was discharged two weeks after admission Venous pressure on admission was 26 cm, but fell in a week to 5 cm The fall in venous pressure preceded a great increase in urine output which came eight days after admission

CASE 8—33,350 A T, aged 44, colored, male Admitted Oct 4, 1914 Clinical diagnosis Myocarditis, myocardial insufficiency Cardiac symptoms began one month before admission with dyspnea, cough and edema Examination showed an enlarged area of cardiac dulness with the signs of myocardial insufficiency Was treated for four weeks and discharged considerably improved Returned to work but in three weeks another break in compensation occurred The patient was readmitted to the hospital with the signs of decompensation Under digitalis, purgation, limited fluids and diuretics the patient's condition was improved and he was discharged after eight weeks in the hospital The venous pressure on first admission varied from 10 to 24 cm and during the second admission (November 22-January 19) varied from 18 to 5 cm, with an average pressure of 10.7 cm

CASE 9—33,166 C A, aged 34, colored, male Admitted Oct 12, 1914 Clinical diagnosis Aortic, mitral and myocardial insufficiency History of rheumatism at 16 years Cardiac symptoms began in August, 1914 Was improved by two weeks' treatment in the hospital Returned to work and had his second break in compensation Was readmitted to the hospital with dyspnea, orthopnea, tachycardia, cough, rusty sputum, râles at both lung bases, an increased area of cardiac dulness and the signs of mitral and aortic insufficiency Improved somewhat by Karell diet, purgation, digitalis and diuretics and was discharged seventeen days after admission The venous pressure varied from 28 to 12 cm between October 15 and 29, with an average pressure of 17.4 cm

CASE 10—33,275 C D, aged 49, white, female Admitted Nov 5, 1914
 Clinical diagnosis Arteriosclerosis, hypertension, myocardial insufficiency, chronic nephritis Housewife with good general health until one year ago when she began having dyspnea, palpitation, orthopnea, edema of the legs and nocturnal polyuria, which became steadily worse On admission, the patient showed albuminuria, a blood pressure of about 200/140, slight edema of the feet, a moderately dilated heart with signs of myocardial insufficiency, and occasional attacks of paroxysmal dyspnea Under digitalis, purgation, diuretics and rest, the patient improved somewhat and was discharged seven weeks later Venous pressure observed from November 12 to December 21 varied from 20 to 9 cm, with an average pressure of 14 cm

CASE 11—33,154 D M, aged 46, white, male Admitted Oct 10, 1914
 Clinical diagnosis Mitral insufficiency, myocardial insufficiency, arteriosclerosis, tuberculosis (?) Aleoholic history Thirteen months before admission began having epigastric pain, shortness of breath and palpitation Admitted with a slightly enlarged liver, mitral disease and doubtful myocardial insufficiency Wassermann positive Suspicious signs of pulmonary tuberculosis Digitalis and limited fluids Discharged eight weeks after admission in improved condition Venous pressure from October 14 to 22 varied from 12 to 8 cm, with an average pressure of 10.4 cm

CASE 12—33,531 J F, aged 42, colored, male Admitted Jan 3, 1915
 Clinical diagnosis Syphilis of aorta, aortic insufficiency Two weeks before admission the patient began having cough, shortness of breath and palpitation On admission the patient was dyspneic and showed the signs of aortic insufficiency and moderate dilatation Wassermann positive Digitalis, purgation and limited fluids Discharged in three weeks with the heart well compensating Venous pressure from January 6 to 24 varied from 22 to 10 cm, with an average pressure of 15.2 cm

CASE 13—T T, aged 42, colored, male Admitted Jan 19, 1915 Clinical diagnosis Myocardial insufficiency and aortic insufficiency Fourth admission to the hospital since March, 1913, for recurrent breaks in cardiac compensation Admitted with dyspnea, orthopnea, edema, moderate ascites and an enlarged heart with the signs of aortic insufficiency Under restricted fluids, purgation and digitalis his condition improved gradually Venous pressure, observed from January 26 to February 16, varied from 20 to 10 cm, with an average pressure of 13.8 cm

CASE 14—33,420 W H G, aged 51, colored, male Admitted Dec 7, 1914
 Clinical diagnosis Myocardial insufficiency, syphilis of aorta Patient had periodic attacks of dyspnea and palpitation for six years before admission but no edema Last attack began five weeks before admission and was accompanied by edema of the ankles and swelling of the abdomen Symptoms became steadily worse and on admission the patient was dyspneic, orthopneic, showed a dilated area of cardiac dulness, auricular fibrillation, a large tender liver, shifting dulness in the flanks, and edema of the ankles Wassermann positive Kirell diet, limited fluids, purgation, digitalis and strophanthin Discharged in five weeks with compensation well established Venous pressure from December 11 to January 10 varied from 22 to 16 cm, with an average pressure of 19 cm

STUDIES ON THE RELATIONS OF THE HYPERSUSCEPTIBILITY AND INSUSCEPTIBILITY INDUCED IN GUINEA-PIGS BY THE INSTILLATION OF HORSE SERUM INTO THE NOSE¹

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In the course of an investigation detailed by one of us a year ago,¹ it was found that when a normal guinea-pig was treated by a series of instillations of horse serum through the nose the results of the treatment, as tested by subsequent intravenous injections of horse serum, were always positive but in two opposite directions. In one group of animals the first intravenous injection of serum caused speedy "anaphylactic" death, that is, the individuals had been highly sensitized to horse serum by the instillations. In the other group of animals the first intravenous injection produced either no reaction or a variable degree of shock, and a second injection after an interval of three weeks was likewise withstood.

We have sought, in the present research, to determine the experimental conditions under which might be produced at will either increased specific sensitiveness or magnified resistance to the operation of the antigen.

It seemed as if the modification of vital irritability into hypersensitiveness or hyposensitiveness might depend on the time interval elapsing between successive serum treatments, therefore the first task we set ourselves was to determine the effect of varying this interval as measured by the reaction of the guinea-pig to subsequent intravenous injection.

The antigen used by us was uniformly the "normal horse serum" prepared at the Cutter Laboratory, Berkeley, California.

There are strong *a priori* reasons why the mucous membrane of the nose deserves especial consideration as an avenue through which the immunological processes of the organism may be set in motion. It seems to us to be the organ, *par excellence*, through which the *natural* reactions between antigens and the living tissues are mediated. An animal could conceivably die of old age without ever experiencing an infective scratch of the skin, but every breath of air inhaled contains its suspension of organic matter liable to settle on the nasal channel.

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¹ Sewall THE ARCHIVES INT MED, 1914, LIII, 856

and there set up profound reactions. Moreover, it seems probable that the dosage of serum absorbed through the application of a few drops to the mucous membrane of the nose must belong to the same order of values as the noxa of pathogenic germs which play so large a part in the infective disorders of man. We must suspect that the biological reactions in the one case are closely paralleled by those of the other.

A single instillation of foreign serum does not, as tested by subsequent "toxic" injections of the same antigen, have any effect that we have been able to discover. But when, at most, five successive instillations have been made, even at intervals of twenty-four days, the results are positive enough. We may say then that each stimulus conveyed in the serum treatment is subminimal in intensity but that the tissues have the ability to summate the effects of individual stimuli and thus be brought to manifest definite reactions, much as the spinal cord is able to integrate the effects of discrete subminimal electric shocks and set forth a reflex action. It seems reasonable to suppose that biologic problems are simplified in proportion to the diminution in intensity and number of reactions entering into them.

LITERATURE

Observations are not wanting on the effects of the introduction of antigen by the natural channels of the body.² Sensitization to proteins has been accomplished by their application to various mucous membranes, as that of the eye, the nose, the stomach, the rectum. There is, however, a note of uncertainty in the claims of those who have used these avenues of sensitization, especially is this so in the description of the effects of oral administration of antigens, their sensitizing properties being often annulled by the action of the digestive juices.

Only among those who, like Dzerjgowsky³ and Blumenau,⁴ have practiced immunization through the nose do we find enthusiastic advocates of the choice of what may be called "physiological" channels of sensitization.

Trenchant evidence that absorption of an antigen through the mucous membrane of the nose determines a biological response different in degree if not in kind from that of the same antigen injected beneath the skin is presented by the experiments of various observers:

2 For literature see Kolle and Wassermann *Handbuch d. path. Mikroorg.* 1913 II 1, 134, 136. Also Vaughan's "Protein Split Products."

3 Dzerjgowsky *Ztschr. f. Immunitätsforsch.* (abstr.) 1910 III, 602.

4 Blumenau *Ztschr. f. Immunitätsforsch.* Ref. Bd., 1911 pp. 196, 353, 860, *Jahrb. f. Kinderh.*, 1911 LVII, 141.

5 Anderson *Bull. 30 Hyg. Lab.* 1906.

with diphtheria toxin Anderson⁵ tried in vain to immunize guinea-pigs to diphtheria toxin by subcutaneous injection He writes

Doses considerably less than the M L D and not sufficient to cause a perceptible reaction were given at intervals of about seven days Before an amount equal to an M L D had been given the animals in each case died These results are in exact accord with the work of Behring and Kitashima, who found that guinea-pigs, when given daily injections of diphtheria toxin and when the total amount injected was only 1/400 of an M L D after a time died with the postmortem lesions of poisoning from diphtheria toxin Instead of being able to produce an immunity to the toxin a hypersusceptibility was produced

Dzerjgowsky³ found it possible to achieve in man and animals a mild degree of active immunity by carefully conducted subcutaneous injections of diphtheria toxin carried on over many months, nevertheless he became the enthusiastic pioneer in the field of absorption by the mucous membranes of the respiratory passages In his work diphtheria toxin was inhaled in sprays or administered on cotton plugs soaked with *undiluted toxin* placed in the nostrils Blumenau⁴ repeated these observations in various ways on a large number of children In one series of experiments, cotton plugs heavily soaked with undiluted toxin were placed for an hour daily in alternate nostrils for a period of one or two weeks Like his predecessor, he found the procedure to cause no subjective symptoms but to be followed by the appearance of a small amount of antitoxin in the blood

Scheweileff⁶ carried out similar experiments on dogs and found he could produce active immunization against diphtheria

The incubation period following an inoculation and preceding the full development of hypersensitiveness probably depends on the dosage of antigen Though Rosenau and Anderson⁷ could find no difference in the incubation period with varying dosage, more recent opinions are in accord that with very small doses of antigen, approaching the minimal capable of producing effect, the latent period of sensitization is greatly prolonged

While a guinea-pig injected with a moderate amount of foreign protein reaches, according to Besredka,⁸ a fairly complete degree of sensitization in twelve days, Weil⁹ found that when 0.01 c c of horse serum was given subcutaneously full sensitization was not manifested by the guinea-pig until the lapse of sixteen days Especially useful to our present purpose is the research of Doerr and Russ¹⁰ These authors treated guinea-pigs with subcutaneous injections of ox-serum

6 Scheweileff Ztschr f Immunitätsforsch, Ref Bd, 1910, x, 1085

7 Rosenau and Anderson Jour Med Research, 1908, xx, 37

8 Besredka and Steinhardt Ann de l'Inst Pasteur, 1907, xxi, 384

9 Weil Jour Med Research, 1913-14, xxix, 233

10 Doerr and Russ Ztschr f Immunitätsforsch, 1909, ii, 109

They found that animals treated with sensitizing doses of from 0.01 cc to 0.001 cc invariably succumbed to the intravenous injection of 0.2 cc of serum after eight days. With sensitizing doses of 0.001 to 0.00001 cc the toxic injection was not fatal until the lapse of nineteen to twenty-five days.

The subcutaneous injection of 0.000,001 cc ($1/1,000,000$ cc) did not cause hypersensitiveness at all. They call attention to the enormous difference between the minimal sensitizing and the minimal (fatal) toxic dose, the ratio being 1 to 1,000.

Rosenau and Anderson¹¹ found that guinea-pigs could be occasionally sensitized by a subcutaneous injection of 0.000,001 cc horse serum. White and Avery¹² say that guinea-pigs when sensitized by the intraperitoneal injection of 0.000,0001 gm of edestin react fatally to the intravenous injection of 0.05 gm of edestin after twenty-one days.

Since in our work only negative results were obtained after a single nasal instillation of serum while profound effects could follow two successive instillations, we may possibly be justified in assuming that the amount of antigen absorbed at each instillation was approximately 0.000,001 gm.

Authors agree fairly well that free antibodies first appear in the blood of an inoculated animal after a latent period of eight to ten days. Wells¹³ summarizes the evidence as follows:

In active sensitization it [anaphylactin—the antibody] appears in the blood in appreciable quantities in about eight days after the sensitizing injection, increases to a maximum between the fifteenth and thirtieth days, and then very slowly decreases.

Dale¹⁴ found that in the uterus of young guinea-pigs sensitized to 0.1 cc horse serum, tested in vitro as to their sensibility to horse serum, up to and including the sixth day (after the sensitizing dose) there was no sign of response to the highest dose employed. On the eighth day one horn of the uterus gave a trifling and doubtful response. On the tenth day the reaction was much more obvious and on the twelfth and fourteenth days the response was maximal.

Besredka and Steinhardt⁸ investigated on guinea-pigs the effect of massive, 2 to 5 cc, intraperitoneal injections of horse serum given at various periods after the subcutaneous sensitizing dose. They found that when the second injection was given within twenty-four hours of the first it had no effect, that is, sensitization proceeded as if from the first dose only. When the second injection followed the

11 Rosenau and Anderson. Bull. 29, Hyg. Lab., 1906.

12 White and Avery. Jour. Infect. Dis., 1913, *vi*, 103.

13 Wells. Chemical Pathology, 1914, p. 185.

14 Dale. Jour. Pharm. and Exper. Therap., 1913 *iv*, 167.

first later than one day and within any period up to twelve days the animal, while manifesting no reaction, became "vaccinated" against the serum and refractory to a subsequent inoculation. A succession of massive intraperitoneal injections given, say, at eight-day intervals, likewise made the animals refractory. They consider this insensitive condition to be one of antianaphylaxis in which the animal is desensitized and returned to the normal state. They say that this refractory state may be induced, in a guinea-pig which has received a sensitizing injection, in two ways: either by a second large intracerebral injection of the antigen ($\frac{1}{4}$ c c) given within ten days of the first or by a small ($\frac{1}{40}$ c c) dose given after complete sensitization. The "immunity" conferred by vaccinating a sensitized guinea-pig lasts three months and probably longer.

Besredka's statement that the "desensitizing" injection restores the animal to the normal state cannot hold for cases, such as are described in the present paper, in which a series of separate toxic injections are withstood.

R. Weil¹⁵ found no difference between animals receiving single or multiple sensitizing injections except that in the latter the blood contains more immune bodies. He injected 3 c c foreign serum subcutaneously in guinea-pigs on four successive days. Toxic intravenous injections given on the eighth and eleventh days produced no symptoms. Given from the thirteenth to fifteenth day they killed.

Rosenau and Anderson,¹⁶ after an elaborate investigation, concluded that guinea-pigs injected subcutaneously with a succession of large doses of horse serum within the period of incubation were partially immunized, while by similar treatment with small doses they were only sensitized. These authors gave ten subcutaneous injections of 2 c c of normal horse serum covering a period of seventeen days. In seventeen days thereafter an intraperitoneal injection of 6 c c serum produced only mild symptoms. Five subcutaneous injections of 0.001 c c of serum given within a period of eight days led, in most cases, to fatal shock from a toxic injection after twenty-three days.

METHOD AND SCOPE OF WORK

The introduction of serum into the nose of a guinea-pig is an extremely simple procedure. As described in a previous article,¹ our method was to clasp the animal's head with the left hand and to hold it gently supine on a table. The serum was dropped from an all-glass hypodermic syringe having a blunted needle. We cannot

15 Weil Jour Med Research, 1913, xxviii, 243

16 Rosenau and Anderson Bull 45, Hyg Lab, 1908

pronounce on the minimum quantity of serum sufficient to produce constitutional effects

The serum was used in full strength and as nearly as possible 3 minims (approximately 0.19 c c) was used at each instillation. The droplets of serum were allowed to fall slowly on one or the other nostril, about five minutes being consumed in each instillation.

Usually but one nostril was utilized at one sitting and the other at the next. In this way the animal was allowed a clear breathing space through the experiment. On a few occasions the dose of serum was distributed into both nostrils, thus probably doubling the absorbing surface put in play, this made no noticeable physiological difference. The guinea-pig treated in this way manifests a wide variety of behavior. In our previous work¹ it was stated that there appeared to be a sharp distinction between the reactions exhibited by the wholly normal and the more or less sensitized pig. The characteristic demeanor of the former animal is one of quiescence, the droplets of serum are sucked in as soon as they fall on the naris. In the second there is a good deal of nasal irritability, the serum excites sniffing and expulsive movements and more or less violent struggles of the whole body.

Several hundreds of additional observations, however, have shown that often wholly normal animals would manifest considerable irritation with the first application of serum while those that had been treated remained quiescent during subsequent instillations. A very common reaction, occurring at both the first and the subsequent treatments, was the secretion of saliva which would well out from the mouth within a few seconds of the instillation of three or four droplets of serum. This excessive secretion of saliva is probably habitual, but its accumulation is prevented by swallowing movements.

The foregoing description applies to reactions from animals treated regularly at intervals less than twenty-four days. More characteristic symptoms are apt to be manifested by pigs which, after daily treatment for three or four times, are allowed to rest for sixteen days before the next instillation, or by pigs at about the fourth treatment in a series with twenty-four days' interval.

More especially in such cases characteristic symptoms of sensitization appear. Two or three minutes after beginning the instillation, more or less active movements of intestinal peristalsis are seen. If the pig is a noticeably pregnant female, twitching of the lower abdominal wall is obvious and if pregnancy is far advanced, within a few days of term, there are very lively fetal movements which seem, when felt by the hand, to be active fetal contractions. We have not been able to assure ourselves that these movements are not imparted

to the fetus by vigorous uterine contractions. The distinction is one of theoretical importance and the question deserves special investigation. During the fetal turmoil the mother remains passive. Succeeding the onset of intestinal peristalsis the respiratory movements are apt to become deeper, and in about one-fifth or more of the cases clicking râles are felt in the throat, then râles are heard in the nose and extend to the bronchial tubes, the animal coughs, becomes dyspneic and is involved in the throes of a bronchial asthma which is almost identical in its symptoms with an asthmatic attack in the human subject. The respiratory urgency gradually passes off in about half an hour, but the animal may still be disturbed after several hours. We can state definitely that the more marked are these signs of *quasi* local sensitization the more likely is the animal to succumb to the toxic injection.

In pigs which have been highly sensitized by a single subcutaneous injection, serum dropped into the nose is apt to cause, after a certain number of treatments, immediate frantic signs of distress to be succeeded in a few minutes by an urgent asthma.

It might be objected that the introduction of an antigen by the nose gives no assurance of the site of its absorption. Some of it may reach the trachea and some is certainly swallowed. We can only say that nothing could be more positive and constant than the systemic reactions that follow such procedures as we describe, whereas the results of those who have sought to sensitize by the stomach seem to be very variable.

In our work already quoted¹ it was proved that the olfactory apparatus per se has no necessary relations to the sensitizing effects of serum introduced into the nose. Also it was found that specific differences marked the reactions resulting from the nasal instillation of horse serum and inhalation of the serum in a spray. Rosenau and Anderson¹⁶ describe a mild degree of sensitization resulting from the instillation of serum into the conjunctival sacs of guinea-pigs. It is obvious, of course, that the antigen might have produced its effect through the nasal mucous membrane after traversing the tear duct.

It is futile to speculate as to the mode of action of the mechanism of absorption. The mucous membrane of the nose presents an immense colloidal surface, which we may imagine to adsorb the foreign protein and give it off little by little to the circulation.

The experimental evidence is positive that specific reactions occur, in certain animals, within about one to three minutes of the time of beginning a treatment by instillation.

Our guinea-pigs were divided into various groups, each of which was utilized in the solution of a definite problem. The first nasal instillation was by the right nostril, the second, after a predetermined

interval of from one to twenty-four days, was by the left nostril, and so on in alternation until the desired number of instillations had been given. Sixteen days after the last instillation there was given an intravenous injection of 6 minims, approximately 0.4 c.c., of horse serum. The absence of a reaction might indicate either a refractory condition of the animal or that the instillation had had no demonstrable effect. Therefore, in case of survival, a second intravenous injection of the same amount of serum was given twenty-four days after the first. When the animal still survived, subsequent intravenous injections were given at irregular, longer intervals up to more than one hundred days.

The injections were made under such light ether anesthesia that when no shock was produced, the animal sat up at once and behaved about as normal as soon as released from the holder.

Friedberger and Mita¹⁷ found that when intravenous injections were carried out with sufficient slowness, through ten minutes or longer, a large amount of serum might be tolerated by sensitized animals. In our later work the time occupied in injecting the serum was regulated. Our usual injection period for six minims of serum was thirty seconds. This period was frequently doubled or trebled, without, in most cases, apparent influence on the result.

The operative technic was carried out wholly by one of us (C. P.) who found that the preferable intravenous route was in a small vein found constantly just under the skin of the upper foreleg. When the guinea-pig is stretched on its back an incision made along the uppermost border of the leg lays this vein bare. The thin sheath is cleared from its upper surface, but the vein is allowed to remain in its bed. The leg of the animal being free, the operator clasps it with the left hand, retracting the lips of the wound with finger and thumb. A fine, sharp hypodermic needle attached to a glass syringe is inserted, the vein being held only by its natural attachments, and the serum injected toward the heart. The minute puncture is closed by passing the first stitch under its site.

The guinea-pig which has been highly sensitized by subcutaneous injection, on receiving an intravenous dose of the antigen quickly shows respiratory distress, deep forced breathing movements, but speedily, in addition, general convulsions usually involve the whole musculature of the body, the spasms having no sensible connection with the respiratory function. In animals sensitized through the nose the general anaphylactic convulsion is much less pronounced. The distress limits itself more nearly to the respiratory apparatus. A pig

¹⁷ Friedberger and Mita. *Deutsch med Wchnschr.*, 1912, *xxxviii*, 204.

may throw a forward somersault in an obvious effort to get the air out of its lungs. On several occasions we are confident that we have saved the lives of badly shocked pigs by compressing their chests with the hand, the air being expelled with a moist, whistling sound. This procedure is in most cases entirely ineffective. The experience suggests however, that in certain cases of anaphylactic shock—at least in the nose-treated animals—death is due not to a toxemia but simply to mechanical interference with lung ventilation. The fortunate outcome of the application of suitable artificial respiration suggests similar treatment in certain human accidents.

We have never seen a delayed toxic reaction in our nasally treated guinea-pigs. In other cases which we have seen in which death was deferred for an hour or more after the toxic injection the lungs did not present the anaphylactic distention. We wish to imply that in the nasally treated pigs anaphylactic fatality seemed to depend on mechanical obstruction to the air exchange without evidence of toxic changes in the vital centers. Gay and Southard¹⁸ have presented interesting observations in this connection.

ORIGINAL EXPERIMENTS

The results of our first set of observations are summarized in Table 1. As our object was primarily to determine the specific influence of the interval elapsing between successive instillations our animals were divided into groups on this basis.

In Column 4 the intervals in days between successive instillations are recorded, with a few noted exceptions the two nostrils were treated in alternation. Each animal is identified by a number in Column 1. The weight of each animal in grams is recorded at the beginning and again at the end of its experimental career. The results following the intravenous or "toxic" injections of serum are recorded in Columns 6 to 10. When an animal survived such an injection (L) the degree of reaction manifested is represented by the signs + (one or more) and 0, 0 signifies no perceptible effect—the animal sits up at once after release from the holder and behaves altogether normally except for possible signs of weakness, ether was administered only sufficiently to dull the operative pain. The sign + signifies slight reaction such as might be manifested by the animal lying on its side for a few minutes with somewhat dyspneic breathing. Severer but not dangerous symptoms are characterized by ++, indicating a moderate reaction. Finally, a certain number of animals recovered after manifesting most violent distress, which evidently had its origin in

¹⁸ Gay and Southard Jour. Med. Research, 1908, xix, 17

TABLE 1—RESULTS OF INTRAVENOUS INJECTIONS OF HORSE SLRUM FOLLOWING COURSES OF INSTALLATIONS OF SLRUM INTO THE NOSE IN GUINEA-PIGS

1 Pig No	2 Sex	3 Weight at Outset, Gm	Installations*		Intravenous Injections†										11 Final Weight Gm	12 Remarks
			4 Inter vals Be- tween, Days	5 Total Num- ber	6 First Results	7 Second Results	8 Third		9 Fourth			10 Fifth				
							Results	Days After 2d	Results	Amt Serum cc	Days After 3d	Results	Amt Serum cc	Days After 4th		
1	♂	270	2	6	L +	L +++	L ++	73	L +		69	L +			815	Note in Column 10 more than double the usual toxic dose Pig died through accident
2	♀	270	2	6	L 0	L ++	L ++	82	L 0?		69	L 0?	0.88	37	810	
3	♂	270	2	6	L +	L +++									?	
4	♂	210	2	6	L +?	D									510	
5	♀	180	2	6	D										360	
6	♀	180	2	6	L +	L ++	D								660	
7	♀	510	2	6	D										600	
8	♀	510	2	6	D										660	
9	♀	270	1	6	L +	L +++	L +	39	L 0		93	L 0			780	
10	♂	300	4	6	D										480	
11	♀	210	1	6	D										180	Died from accident
12	♂	180	1	6	L +										420	
13	♂	180	1	6	D										?	
14	♀	260	1	6	D										?	
15	?	260	5	6	D										?	
16	♂	210	5	6	D										?	
17	♂	210	5	6	L +++	L ++	L +	31	L 0		93	L 0			930	
18	?	180	6	6	L +	L ++?	D	17							780	
19	♂	210	6	6	D										510	
20		180	6	6	L +										180	

mechanical obstruction to the respiration, these are indicated by +++

Practically all our fatalities occurred within four minutes of completing the injection. Necropsy in every case but one showed the lungs in characteristic distention. Manifestly, if a guinea-pig fails to react to the first toxic injection it may be either because sensitization has not been achieved or because the animal is refractory. Therefore a second toxic injection is necessary and to this the animal, in the first case, should succumb.

Following the second toxic injection, subsequent injections were made at various prolonged intervals and with the use at times of an increased amount of serum, up to thrice that selected as the ordinary "toxic" dose.

A glance at the table shows (Column 6) that, of forty-one animals treated by the nasal instillation of serum, twenty survived the first toxic injection. Of these twenty, five gave no positive evidence of sensitization but all of these survived a second toxic injection or more. Twelve animals showed slight reaction to the first toxic injection. One of these died shortly after from trauma and one succumbed to the second toxic injection, all the rest survived it. Of the remaining three surviving pigs, two exhibited moderate and one severe shock. Inspection of the table shows that of seventeen animals submitted to a second toxic injection twenty-four days after the first, thirteen survived it with a general increase in intensity of anaphylactic response. Further repetitions of intravenous injection were marked, as a rule, by rapidly declining sensitiveness, whatever the amount of serum used. Possibly the construction of the table may be made clearer by definitely tracing the history of a single animal.

Thus, Guinea-Pig 2 was a female and weighed at the time of the first nasal instillation of serum 270 grams. She received six treatments at intervals of two days. Sixteen days after the last instillation the pig received an intravenous injection of 6 minims (about 0.38 c.c.) of normal horse serum. The animal survived this toxic injection with no perceptible evidences of shock, indicated by the cipher (0). The second toxic injection of 0.38 c.c. of serum given twenty-four days after the first, was survived after a moderately severe reaction. Eighty-two days after the second toxic injection a third was given resulting in moderate reaction. Sixty-nine days later still a fourth injection caused no certain reaction. After waiting thirty-seven days further the pig received a fifth intravenous injection, but now the amount of serum introduced was 0.88 c.c., more than twice the quantity employed in previous injections. There was no reaction whatever.

Study of Table 1 recalls the caution suggested by Rosenau and Anderson against drawing inferences from too meager material in immunization experiments. But even so small a number of observations as ours suggests certain reasonable conclusions. When animals treated precisely alike, as our Guinea-Pigs 1 to 8, manifest the widest possible difference in reactivity to a toxic injection of antigen, we are impressed with the importance of the individual biologic factor.

It seems probable from the evidence offered in Table 1, which is supported by many other experiments, that the biologic attitude respecting the antigen, induced in the guinea-pig by the nasal instillation of serum, is a labile state and may be changed by further similar treatment. Thus, of our animals 1 to 8, treated on alternate days with six doses of serum, five survived the first toxic injection, while three animals (27 to 29), treated twelve times on alternate days, all died with the toxic injection. In contrast to this biologic lability induced by absorption of small doses of antigen, we shall later contrast the vital stability achieved by animals receiving in addition large doses of serum. This important distinction has received the attention of other observers, notably Schultz, Weil and Gurd.

The Influence of Rhythm in the Sequence of Nasal Instillations

The results of experiments in this direction are summarized in Table 2. The observations are, of course, far too limited a number to serve as basis for any hypothesis. This table is constructed on the same lines as the preceding except as to Column 5. Here is shown the order of the nasal treatments. Thus, the first group of two pigs received instillations of serum in alternate nostrils on the first, fourth, fifth, seventh, tenth and eleventh days. Some special interest attaches to the last two groups of three animals each. In the first the order of differences in the intervals of treatment was 4, 3, 2, 1. In the second it was 1, 2, 3, 4. Although the same proportion of animals survived the first toxic injection in each group, there was a markedly intensified resistance in the surviving members (49 and 51), of the last group and it appears that further work on this line is desirable. It is hardly necessary to observe that this field of investigation seems intimately related to that which concerns the spacing of therapeutic vaccines.

The Effects of a Single Instillation and of Two Successive Instillations of Serum

The foregoing results led to the obvious inquiry as to what might be the least number of instillations of serum into the nose which could produce demonstrable reaction. Three minims (0.19 c.c.) of serum were dropped into the nose of each of four young guinea-pigs. Sixteen days later an intravenous injection of 6 minims (0.38 c.c.) caused no

TABLE 2—THE INFLUENCE OF RHYTHM IN THE INTERVALS BETWEEN SUCCESSIVE INSTILLATIONS OF SERUM

Intravenous Injection															
1	2 Sex	3 Weight at Outset, Gm	4 Num- ber of Instilla- tions	5 Se- quence of Instilla- tions, Days	6 First* Results	7 Second† Results	8 Third		9 Fourth		10 Fifth			11 Final Weight Gm	12 Remarks
							Results	Days After 2d	Results	Amt Serum c c	Days After 3d	Results	Amt Serum c c		
42	♀	390	6	1, 4, 5, 7, 10, 11	D									540	
43	♀	390	6	1, 4, 5, 7, 10, 11	D									510	
44	♂	420	6	1, 2, 5, 7, 8, 11	L +	L + +	L +	67						510	
45	♀	420	6	1, 2, 5, 7, 8, 11	D									570	
46	♀	360	5	1, 3, 8, 10, 11	L + + +	D								605	
47	♀	390	5	1, 5, 8, 10, 11	D									540	
48	♂	240	5	1, 5, 8, 10, 11	L +	D								600	Both nostrils instilled at each treatment
49	♂	240	5	1, 2, 4, 7, 11	L + +	L + + +	L + + +	66	D	0.75	82			750	Subcumbled to double the usual toxic dose
50	♀	210	5	1, 2, 4, 7, 11	D									330	
51	♀	210	5	1, 2, 4, 7, 11	L +	L + + +	L +	66	L +	0.5	57	L 0	0.75	750	Bled for serum 31 days after fifth intravenous injection instilled both nostrils

• Sixteen days after last instillation † Twenty four days after first injection

* Sixteen days after last instillation

† Twenty four days after first injection

Both nostrils instilled at each treatment
Succumbed to double the usual toxic dose

Bled for serum 31 days after fifth intravenous injection instilled both nostrils

disturbance whatever When the injection was repeated twenty-four days later the pigs promptly died The same result was obtained whether the serum had been instilled into one or both nostrils

It having been shown that a single instillation of serum is ineffective—that it is, in physiological terms, a stimulus below the threshold of somatic irritability—it concerns us to know whether a second instil-

TABLE 3—THE INFLUENCE OF TWO NASAL INSTILLATIONS OF SERUM AT INTERVALS OF ONE DAY OR MORE

1 Pig No	2 Sex	3 Weight at Outset, Gm	4 Intervals Between Intilla- tions, Days	Intravenous Injection					8 Final Weight
				5 First Results	6 Second Results	7 Third			
						Results	Amount Serum c c	Days After 2d	
52	♂	360	1	L 0	L ++	D		50	720
53	♂	390	1	L +	D				630
54	♂	360	2	L 0	D				690
55	♂	360	2	L 0	D				690
56	♂	300	3	L + ?	D				630
57	♂	275	3	L + ?	D				660
58	♂	270	6—*	L + ?	L 0 ?	D	0 5	28	630
59	♂	300	6—*	L 0 ?	L ++	L —	0 63	80	930
60	♀	270	6	L 0 ?	D				690
61	♂	240	6	L +	D				600
62	♀	240	9	L 0 ?	D				630
63	♂	210	9	L 0 ?	D				540
64	♀	270	9—	D					480
65	♀	270	9—	D					480
66	♂	210	12	D					420
67	♂	180	12	L 0 ?	D				540
68	♀	210	14—	L ++	D				630
69	♂	240	14—	D					450
70	♂	270	14—	L 0	D				630
71	♀	210	16	L +	D				600
72	♂	180	16	L 0 ?	D				600

* In Guinea Pigs 58 and 59 interval between instillations above 3 hours less than 6 days
Note increased resistance of 59 with lapse of time Thirty days after third intravenous injection 59 was bled for serum

lation can summate its influence with the first so as to give rise to distinct reactions and, if so, whether the interval elapsing between the two stimuli is of significance The outcome of our experiments in this direction is depicted in Table 3

Of the twenty-one animals, four promptly died with the first intravenous injection of 0.38 c c, sixteen days after the last instillation of horse serum. In these four the intervals between the two instillations ranged from somewhat less than nine to nearly fourteen days. That is, the periods were presumably sufficient for the production of free antibodies from the first instillation by the time the second was given. Of the seventeen pigs surviving the first toxic injection, four showed no discernible signs of reaction, while in thirteen the result was decidedly positive or doubtful. A second intravenous injection of 0.38 c c serum given twenty-four days after the first was survived by three animals. Pig 52 had shown no reaction with the first toxic injection, was moderately but not dangerously infected with the second but succumbed to a third, which followed the second in fifty days.

TABLE 4—THE INFLUENCE OF TWO NASAL INSTILLATIONS OF 0.19 CC SERUM AT INTERVALS OF FROM FIFTEEN TO THIRTY HOURS

1 Pig No	2 Sex	3 Weight at Outset, Gm	4 Inter vals Between Instilla tions, Hours	5 Intra venous Injec tion First Results	6 Intra venous Injec tion, Second Results	7 Final Weight	8 Remarks
73	♀	270	15	D		420	Intravenous injection = 0.25 c c serum
74	♀	300	15	L 0 ?	D	630	
75	♀	300	19	D		?	
76	♀	270	20	L 0 ?	D	630	
77	♂	240	20	L + ?	D	570	
78	♂	240	25	L + ?	D	540	Lungs nearly collapsed at necropsy
79	♂	270	25	D		420	
80	♀	270	30	L + ?	D	690	
81	♂	270	30	L 0 ?	D	570	

Pigs 58 and 59 survived two intravenous injections. No 58 succumbed to a third injection twenty-eight days after the second, the amount of serum injected having been increased to 0.5 c c, one and one-fourth times the usual dose. Pig 59, which had reacted much more plainly than the preceding to the second toxic injection, did not receive the third intravenous injection until the lapse of eighty days, when it hardly reacted to the injection of 0.63 c c serum, one and two-thirds the usual amount. Thirty days after its third intravenous injection this pig was bled and its serum injected into normal animals with results that will be described later.

The general conclusions from this group of experiments are that two nasal instillations of serum separated by intervals of one to sixteen

days usually demonstrably modify somatic irritability and that such modification may be profound even when a large toxic injection gives negative results

The curious protection manifested by Pig 52, which had received nasal treatments separated by about twenty-four hours, made advisable a more careful study of the effect of two instillations separated by small intervals of time. In Table 4 are condensed the results of experiments on nine animals, each of which received two instillations separated by intervals of from fifteen to thirty hours. Of the six pigs surviving the first toxic injection, three gave positive and three doubtful signs of sensitization, but none were made refractory. It is worth noting that on necropsy the lungs of Pig 79 were found nearly collapsed and that they *seemed* to expand slightly later.

It is plain from the foregoing that the fundamental question why certain animals become sensitized and others are made refractory by nasal instillations of serum is definitely answered neither by the spacing of the treatments nor by the rhythm of their succession, although these factors apparently have an important bearing on the results. On further reflection it seemed as though the varied results of different series of instillations might easily be accounted for. Thus, it is reasonable to suppose that the state of sensitization developed by any instillation of serum would be annulled by the next succeeding treatment, following the well-known conditions of desensitization, and that a subsequent toxic injection would be tolerated. According to this idea, when a series of instillations is given spaced so as to allow each treatment to exercise its full effect before the next is applied, the animals receiving an even number of treatments should all survive the first toxic injection, while those subjected to an odd number of instillations should succumb to the injections. This view seemed supported by the remarkable resistance exhibited by Pigs 21 to 23 of Table 1, which had received six instillations at intervals of fourteen days, compared with the hypersusceptibility of Pigs 36 to 41, which had received but five instillations. In experimental test of this theory it seemed reasonable to consider all instillations obviously falling within the incubation period of the first as a single treatment.

Twelve guinea-pigs, accordingly, were divided into four groups, each of which was given five instillations of serum spaced as shown in Table 5.

In Group 1, it was assumed that the four daily instillations acted essentially as a single larger dose. Twelve days after the last treatment, namely, on the sixteenth day, the final instillation was given. Sixteen days later the toxic injection was given and, according to

theory, should have been withstood, but it was fatal to all three animals. In Group 2, after three instillations we waited twelve days and then gave a fourth treatment on the fifteenth day. This treatment, according to theory, should have desensitized the animal so that the next instillation (in the case of two pigs given on the following and in the remaining animal after two days) should have sensitized the animals and led to fatal results from the first toxic injection. Such indeed was the issue, but it means nothing in view of the result in Group 1. The experiment in Groups 3 and 4 were identical except that sixteen days were allowed to elapse between the cluster of sensitizing instillations and the test instillations. It is noteworthy that of the two pigs surviving the first toxic injection one belonged to each group, though according to theory all of Group 3 should have lived and all of Group 4 should have died. Moreover, a consideration of the

TABLE 5—INFLUENCE OF FIVE NASAL INSTILLATIONS AT VARYING INTERVALS

Group No	Sequence of Five Instillations in Days	Number of Pigs Surviving		
		I V Inj 1*	I V Inj 2†	I V Inj 3‡
1	1, 2, 3, 4, 16	0		
2	1, 2, 3, 15, 16	0		
	1, 2, 3, 15, 17	0		
3	1, 2, 3, 4, 20	1	1	0
4	1, 2, 3, 19, 20	0		
	1, 2, 3, 19, 21	1	0	

* First intravenous injection sixteen days after last instillation, 0.38 c.c.

† Second intravenous injection twenty two days after first, 0.38 c.c.

‡ Third intravenous injection seventeen days after second, 0.5 c.c.

history of Pigs 24 to 26 of Table 1 militates against the theory. These animals had received six instillations of serum at intervals of twenty-four days, yet only one survived the first toxic injection. At the sixth instillation this pig, which had about half completed a period of pregnancy, showed active abdominal peristalsis, while the remaining two suffered severe asthmatic seizures.

It would appear from the foregoing account that, so far as the evidence goes, *the accepted principles of desensitization or antianaphylaxis cannot explain the survival of the first toxic injection by animals which have received a course of serum instillations by the nose.* Even could tolerance to the first toxic injection be accounted for as the result of previous desensitization, the explanation of the survival of the second toxic injection would be rendered possibly more difficult.

The Influence of Nasal Instillation of Serum on Guinea-Pigs Previously Fully Sensitized by Subcutaneous Injection

Such profound effects having been produced by administration of horse serum through the nose in normal guinea-pigs, it was desirable to ascertain if in fully sensitized animals reactivity to toxic injections could be modified by the same treatment. Rosenau and Anderson¹⁰ had already pursued the same idea. They gave to fully sensitized pigs small subcutaneous injections of antigen and could not find any sign of tolerance being established. Similar negative results attended the efforts carried out by one of us in the work referred to.¹

But since this phase of the subject seems to illustrate the conditions determining the rational use of vaccines in disease, and since there seems increasing confidence, especially among rhinologists,¹⁹ in the therapeutic efficacy of local and general administration of antigens in what are apparently anaphylactic disorders, no opportunity should be lost to gather experimental data which might be pertinent to the problem.

Four guinea-pigs were given subcutaneous injections of 0.25 c c horse serum on June 8. July 15 to 19 they were subjected to certain losses of brain tissue without, as determined by controls, essential modification of sensitization. More than fifty days after the sensitizing injections, nasal instillation of serum was begun, each pig receiving twelve doses, two of the animals being treated daily and two on alternate days. Both of the animals receiving daily treatment began to show slight signs of general reaction with the second instillation, as manifested by respiratory râles, cough and labored breathing. With further treatment these reactions developed into very severe paroxysms of asthma which came on a few minutes after beginning instillation, lasted about half an hour and still showed effects after six hours.

With the last few instillations the asthmatic symptoms gradually failed, though signs of local irritation, as nose rubbing, persisted. In our previous work no general symptoms were produced in sensitized pigs by the nasal instillation of serum until about eight days had elapsed after the first instillation. In the foregoing cases general symptoms were elicited after twenty-four hours. It is a question whether the excision of a portion of the brain had anything to do with this shortened latent period.

The reactions of pigs instilled on alternate days pursued a similar course except that the first manifestations of general reactions did not appear until six days after beginning treatment.

These four animals were given intravenous injections of 0.38 c c of serum sixteen days after the last instillation and all promptly died.

¹⁰ Goodale G. J. L. *Ann Otol, Rhinol and Laryngol*, 1914, *xxiii*, 278.

in respiratory anaphylaxis but with a marked absence, for the most part, of the general convulsions usually distinguishing such exitus

From the well-known teachings of Besredka and others it might be supposed that a series of instillations of serum by the nose within the latent period of subcutaneous sensitization might "vaccinate" the animal so that it would tolerate, at least, the first intravenous injection of serum

Two young guinea-pigs, which had suffered operative loss of part of the brain, but were otherwise normal, were given subcutaneously each 0.38 c.c. of horse serum and immediately thereafter 0.19 c.c. of serum were instilled into a nostril of each. Six instillations were given, in one case the treatment being repeated daily and in the other every other day. Sixteen days after the last instillation the pigs received intravenous injection of 0.38 c.c. of serum.

The result was fatal as in the previous group. It may be worth mentioning that the pig receiving daily treatment showed noticeable disturbance of respiration with the second instillation. So far as these experiments go they indicate that the nasal instillation of serum is capable neither of annulling subcutaneous sensitization which is fully developed nor of modifying the process of subcutaneous sensitization when administered during the incubation period.

Hereditary Transmission of the Anaphylactic State

Twenty-nine offspring from our guinea-pigs became available for observation. These fall naturally into three groups.

1. Seven pigs were born to four mothers that had each received subcutaneous injection of 0.25 or more of horse serum. The parents had been subjected to operations on the brain after sensitization. The offspring were tested by intravenous injection of 0.05 to 0.38 horse serum thirty or forty days after birth. All promptly died except one of a litter of three the mother of which had received her subcutaneous injection only thirty-four days before parturition, and therefore within the latter half of the period of gestation. Two of this litter promptly succumbed to the intravenous injection of 0.25 and 0.38 c.c., respectively, the third surviving the injection of 0.12 c.c. The litter was tested on the fortieth day of life. Of the seven animals in this group only one survived the first small intravenous injection.

2. Fourteen of the offspring were from four mothers which, after a course of five or six nasal instillations of serum, had tolerated from one to three intravenous injections of 0.38 c.c. of horse serum. One of the offspring was not tested until the eighty-third day after birth, when it was not affected by the intravenous injection of 0.38 c.c.

horse serum, that is, the passive sensitization had passed off. Two others from the same litter, tested on the thirty-first day, survived the injection of 0.25 and 0.06 c.c. serum, respectively, the former with very severe and the latter with moderate symptoms. But these pigs quickly succumbed to a second intravenous injection fifty-two days after the first. A similar result attended the second injection of all other pigs of this group which survived the first injection, receiving their second injection from twenty-four to eighty-seven days after the first. We must conclude that, for whatever reason the offspring resisted the first toxic injection, it was not because there was transmitted to them an ability to destroy the antigen before it sensitized their tissues. Of the thirteen offspring of this group receiving intravenous injections, usually of 0.25 c.c. or more of serum, within thirty-five days of birth, no less than five survived the first toxic injection.

3 Seven offspring were available from four mothers which had received a course of four or five nasal instillations. None of the parents had been given the toxic injection except two which had received 0.38 c.c. serum in a vein five days before the birth of their young. Five of the seven offspring survived an intravenous injection of 0.25 c.c. serum given nineteen to thirty-three days after birth. All succumbed to a second intravenous injection given seventeen days or more after the first.

It is obvious from the foregoing account that a higher degree of susceptibility is transmitted to their offspring by mothers that have been sensitized by subcutaneous injection than by those that have received a much larger quantity of serum intravenously following courses of nasal instillations. Still more marked is the comparative insusceptibility in the offspring of mothers which had been treated only by the instillation of serum into the nose, though they were subsequently found to be more or less refractory to toxic injections.

In his classic researches on inheritance of sensitization, Ehrlich found it necessary to limit his observations to the offspring of mothers that had already been fully sensitized before the beginning of pregnancy.²⁰ When the parent was sensitized after gestation had set in there was always chance that an active immunity might be conferred on the fetus. The offspring in our experiments were from mothers that had been serum-treated during the term of pregnancy. Nevertheless it is most improbable that the numerous survivals from the first toxic injection could have been due to an active immunity, since all the animals succumbed to the second toxic dose.

²⁰ Morgenroth and Braun. *Handbuch d. path. Mikroorg.*, 1913, II, 2, p. 1155.

Experiments on Normal Guinea-Pigs Which had Received Intraperitoneal Injections of the Serum of our Immune Animals

Immunologists agree that the serum of an immune animal injected into a normal individual renders the latter passively anaphylactic to the antigen used. The higher the degree of immunity possessed by the donor the greater the number of antibodies in its circulation and the smaller the quantity of serum necessary to the transfer of sensitization.

Guinea-Pigs 22 and 23 of Table 1 sustained with practically no reaction a fourth intravenous injection of 113 cc horse serum each 101 days after the third injection. Twenty-four hours later these pigs were bled and their scrums separated in a centrifuge. We are greatly indebted to our colleague, W. C. Mitchell, who kindly volunteered to carry out this phase of our work. The serum from each animal was at once injected into the peritoneal cavities of three normal pigs weighing about 240 grams each. In each lot of three normal pigs one received 0.5 cc, one 20 cc, and one 40 cc or 50 cc of serum.

Two days later the six pigs were given intravenous injections of 0.25 cc horse serum each. All the animals recovered, four had very slight reactions, but in the two which had received only 0.5 cc of serum in the abdomen the reaction was moderately severe. On the whole the anaphylactic phenomena differed widely from those usually witnessed, and resembled exactly the reactions manifested by sensitized pigs after excision of portions of the brain. The animal when released from the holder lies on its side with legs held stiff and involved in clonic tremblings, occasionally grotesque, tetanoid movements of the body occur, very minor, if any, respiratory disturbance is seen. Seventeen days later a second intravenous injection of 0.25 cc horse serum was given each of the six pigs. All died within five minutes except the two pigs which had received the smallest intraperitoneal injection (0.5 cc) and which had responded most strongly to the first toxic injection, these recovered, one after slight and the other after very severe reaction.

Eighteen days later these two animals received a third intravenous injection of 0.25 serum. Both died in four minutes.

According to current notions, these two pigs must have been sensitized by the intraperitoneal injection of 0.5 cc of immune serum and desensitized by the intravenous injection of 0.25 cc serum given two days later, they therefore recovered from the second intravenous injection seventeen days later, but were resensitized by it and succumbed to the third intravenous injection after eighteen days. It is not, however, clear why the much larger amounts of immune serum given the remaining four animals neither sensitized to a lethal anaphylaxis at the first intravenous injection nor protected them from the second toxic injection. Also, it seems extraordinary that so large an amount as 0.25 cc serum should not have sufficed to resensitize strongly the two resistant pigs at the first intravenous injection.

Anderson and Frost²¹ have shown that the "allergen" contained in 3 cc of the serum from a sensitized guinea-pig (an amount capable of sensitizing a normal pig in twenty-four hours) can be neutralized by admixture of an amount of horse serum less than 0.01 cc. It is therefore conjectural how far the sensitizing properties of our immune

21 Anderson and Frost. Bull. 64., Hyg. Lab. 1910.

serum may have been modified by the massive injection of antigen given one day before

Accordingly the experiment was repeated, using as donors Guinea-Pigs 51 of Table 2, which had received a fifth intravenous injection to the amount of 0.75 cc horse serum thirty-one days before, and 59 of Table 3, which had received its third intravenous injection, amounting to 0.63 cc horse serum, eighty days before. The serum from each donor was prepared as in the first case and injected intraperitoneally into three normal pigs having an average weight of 330 grams. From the first donor the quantities of serum injected were 0.5 cc, 1.0 cc and 9.0 cc. From the second donor the amounts injected were 0.5 cc, 1.0 cc and 4.5 cc. Twenty-three hours later each of the recipient pigs was given an intravenous injection of 0.25 cc horse serum. All recovered after very slight reaction, the response being most marked in the pig which had received 9 cc serum in the abdomen.

Sixteen days later these six animals were given a second intravenous injection of 0.25 cc horse serum. All died after manifesting, with one exception, unusual tendency to recover. The struggles of the pig which had received 9 cc of serum were unique in intensity and duration, persisting about eighteen minutes before the animal succumbed. Strange to say, at necropsy the lungs in this case were semi-collapsed.

The only work we know that bears on this subject is that recently published by Gurd, who insists on the "presence in the circulating blood of immune animals of bodies which are potent to induce the hypersensitive state when introduced into normal animals and also of bodies which if injected in sufficient quantities are able to render normal animals immune."

Subsequent inoculation [of an injected animal] in sublethal doses results in the stimulation of the production of a second order of ferments whose activity is directed more particularly toward the more complete cleavage of the toxic split product."²²

Gurd concludes that the injection into normal guinea-pigs of small amounts of immune serum sensitizes, while injection of large amounts renders them refractory. It may be remembered that in our first experiment under this head exactly the opposite was noted. We fail to see how Gurd's main conclusion is justified by his protocols. Further discussion of this subject will be deferred for the present.

Specific Tissue Resistance as a Factor in Immunity

We have shown that a few applications of horse serum to the mucous membrane of the nose in the guinea-pig profoundly modifies

²² Gurd, F. B. Jour. Med. Research, 1914, XXVI, 205

the organism That a toxic injection of serum following such a course of treatment should be attended by signs of sensitization or death is wholly to be expected from our present conception of immunity processes When, however, as in Pigs 2, 21 and 23 of Table 1, the first toxic injection is not only negative but fails to render the animal fatally anaphylactic to a second intravenous injection given twenty-four days later, it is obvious that the animal has been in some way positively protected by a biological modification induced by the nasal instillations of serum

Since it is seen in the case of Pigs 52, 58 and 59 of Table 3 that such protection may be manifested by so few as two instillations separated by an interval of less than six days, it would seem that the anaphylactic antibody as usually understood could have no essential part in the protection for, according to all evidence, such antibody is not yet formed

In the preceding section we have shown that we may suspect the existence of something in the serum of highly immunized guinea-pigs which when introduced into the normal animal protects it from the usual reactions of passive anaphylaxis Gurd has already dwelt on this conception, but an essential feature of Gurd's protective body is its late formation in the course of immunization It is conceivable that the relatively refractory state of some of our animals should be produced by a specific protective substance developed as a reaction to even two nasal instillations of serum In other words, we are confronted with the possible existence of two different offspring of biologic reactivity, one the familiar *allergic* antibody and the other an as yet undefined *resistance* antibody

We have no intention at this time to assume, except as a working hypothesis, so far-reaching a conception

But there is another possibility in support of which we will hazard a course of reasoning before offering experimental evidence

It seems to us that immunologists have not laid due stress on the autonomy of the living tissues as a factor in immunity Living tissues exhibit a marked resistance against digestion by proteolytic enzymes that actively attack them dead²³ According to Wells² "snakes are nearly or quite insusceptible to snake venom Cunningham found that the serum of cobras was devoid of antitoxic property, so that the immunity of snakes must be ascribed to an absence of cell receptors in their tissues with which their venom amboceptor can combine" Roosevelt,²⁴ from another point of view, makes observations differing only in detail There is, then, no *a priori* reason for

23 Wells Chemical Pathology, 1914, pp 62, 147

24 Roosevelt, T Through the Brazilian Wilderness, 1914, p 9

denying to the tissues extreme plastic power, but it remains to prove that modification of tissue resistance is a part of the condition of immunity. The following observations lend strong support to such a view. In his numerous experiments supporting the cellular theory of immunity, R. Weil found often an extraordinary difference in reactivity to the antigen to be exhibited by the two horns of the uterus in the sensitized guinea-pig, that is, the avidity of the same tissue for the antibody is widely variable.

In his latest paper Weil²⁵ holds that the antibody attached to the tissue cell must become "activated" by the latter before it becomes capable of causing anaphylactic reactions with the antigen, a view which recalls the hypothesis of Friedemann,²⁶ according to which the antibody exists as a zymogen which is activated by contact with antigen.

Schultz,²⁷ in his pioneer work on the anaphylactic reactions of isolated muscular tissues, found that,

Guinea-pigs that have been rendered tolerant to large doses of serum by repeated injections of serum yield muscle that reacts much like that from sensitized animals even when 1 cc intravenous injections cause no more prominent body reactions than those observed in normal animals.

In time, however, this protective mechanism becomes less efficient and an injection of serum may cause anaphylactic symptoms in the intact animal.

In his careful and well-known work on the same subject Dale²⁸ confirms these findings, but in addition relates a curious experience which seems to us of great significance. According to Dale, when guinea-pigs immunized by multiple injections of serum were kept a long time (say three months) after the last injection, the uterus taken from such animals were nearly insensitive to the action of horse serum, although the controls showed evidence of abundant antibodies in their circulation.

This observation led us to test definitely on our animals the influence of the time element on anaphylactic reaction. Our Guinea-Pigs 21, 22 and 23 had each received a third intravenous injection of 0.38 cc of horse serum on a certain date without reaction. Thirty-six days thereafter Pig 21 was given a fourth intravenous injection, of which the amount was increased to about 1.1 cc. The animal recovered, after nearly dying from the shock. The remaining two pigs were kept for 101 days before receiving their fourth toxic injection of 1.13 cc serum. This they withstood with scarcely noticeable signs of reaction.

25 Weil Jour Med Research, 1915, xvi, 107

26 Friedemann, U. Ztschr f Immunitätsforsch, 1909, ii, 591

27 Schultz Bull SO, Hyg Lab, 1912

28 Dale Jour Pharmacol and Exper Therap, 1913, iv, 167

It was the slightrness of the response obtained from the massive intravenous injection in these pigs which led to a test of the antibody content of their serum which has already been described. Gay and Southard lay stress on their findings that animals rendered "immune," usually by large spaced injections of serum, reacquire sensitivity and "eventually become quite as susceptible as do animals which have had a small initial dose, the incubation period varying directly with the amount injected on the first dose or doses. It seemed more correct then, to refer to these animals as 'refractory' rather than 'immune.' It was furthermore noted that the offspring of such refractory animals, born during a period of full refractoriness in the mother, were not themselves refractory, but sensitive to intoxication by horse serum."²⁹ These lines are quoted to show how utterly different are the results of our parallel experiments performed on animals receiving an initial course of treatment through the nose.

Similar results were obtained in comparing Pigs 58 and 59 of Table 3. Pig 58 had received a second intravenous injection of 0.38 c c serum without obvious reaction, but twenty-eight days later succumbed to a third injection increased to 0.5 c c. Pig 59, which had otherwise been treated just like 58 and had reacted much more sensibly to the second toxic injection, was kept for eighty days and then received its third intravenous dose, which was increased to 0.63 c c, but responded with only slight reaction. Unfortunately the basic idea of this discussion did not develop until most of our animals appropriate to the investigation had been disposed of. Nevertheless a glance at the tables will show that Pigs 9, 17 and 44 showed no signs of reacquired sensitivity to the intravenous injection of 0.38 c c horse serum after resting periods of two or three months. Pigs 18, 32, 49 and 52 died at the third or fourth toxic injection. It should be noted, however, that in two of these cases the amount of serum injected had been increased to 0.75 and 1.0 c c.

The outcome of these experiments seems to controvert Weil's view³⁰ that the protecting agency in cellular immunity is the antigen contained in the tissues which, gradually disappearing, allows the cells finally to regain their sensitiveness. It would rather appear that metabolism of antigen within the cells enables the latter to assume a resistance to the toxic substance as an essential end result of the process of immunization. The inference is obvious that the existence of the immune carrier of disease is in some way based on such tissue resistance as has been experimentally illustrated above. The results obtained in the experiments last described recall data presented by

29 Gay and Southard Jour Med Research, 1908, xviii, 407

30 Weil Jour Med Research, 1914, xxx, 347

Rosenau and Anderson¹⁶ some years ago. These authors treated guinea-pigs with serial subcutaneous injections of horse serum to total amounts of 30 to 60 c c.

The animals were kept as long as 249 days when each received an intracerebral injection of about 0.2 c c horse serum. The pigs reacted slightly or not at all. Two hours later the animals were bled and from 5 to 12 c c of the serum was injected subcutaneously into normal pigs. These were tested intracerebrally as before and each showed slight to marked symptoms.

Hektoen³¹ calls attention to the established experience that "in actively immunized animals immunity may persist after the new antibodies have passed out of the blood."

SUMMARY

When a few drops of horse serum are instilled into the nose in guinea-pigs and the dose is repeated from one to five times at intervals varying from one to twenty-four days, about one-half the animals survive an intravenous injection of horse serum given sixteen days after the last instillation.

This survival is sometimes without symptoms, but cannot be due to previous desensitization, for a second intravenous injection is frequently well borne twenty-four days after the first.

We have tried in vain to find the conditions according to which the course of nasal instillations produce, on the one hand, the hypersensitive or, on the other, the refractory state. The accepted principles of desensitization do not account for the facts.

When, after several intravenous injections of 0.38 c c of horse serum guinea-pigs fail to react, the dose may, in certain cases, be doubled or trebled with like result.

Contrary to the usual experience, we have found in two groups of refractory animals that a large intravenous injection was better borne after a resting period of 101 days and 80 days, respectively, than in controls after 36 and 28 days.

When the blood serum of these immune animals was injected intraperitoneally into normal guinea-pigs, the latter, when given 0.25 c c serum by the vein twenty-three to forty-eight hours afterward, usually reacted very slightly. Two animals injected with 0.5 c c of serum into the abdomen showed stronger reaction to the toxic injection than those given 4 or 5 c c. Also, they withstood a second intravenous injection after seventeen days to which the rest succumbed.

³¹ Hektoen, L. in Musser and Kelly's Practical Treatment, 1911, 1, 256

As is well known, the offspring of mothers sensitized by a single subcutaneous dose of serum are themselves highly sensitive to a small toxic dose of serum given within about six weeks

In our animals treated by instillation only, five out of seven of the offspring survived the toxic injection

It is a pleasure to express our indebtedness to Dr W C Mitchell and Dr R G Morrison for essential aid in these experiments

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CHANGES IN THE P WAVE OF THE HUMAN ELECTROCARDIOGRAM *

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The most important observations in regard to the "P" wave of the human electrocardiogram have been those concerning its changes in mitral stenosis. Various workers, including Einthoven,¹ Krauss and Nicolai,² and Samjolloff,³ have called attention to an increase in height and often also a broadening of the P wave in this disease. To quote the last

Wir fanden ebenfalls bei Mitralstenose Verstärkung und meist auch Verlängerung der P-Erhebung (We found likewise in mitral stenosis an augmentation, and generally also a prolongation of the P wave)

Since the increase in the height of the P wave has been thought due to the auricular hypertrophy resulting from the narrowing of the mitral ring, it would be reasonable to believe that auricular hypertrophy, the result of any other pathological change, would have the same effect. Hence it has been the custom at this station to consider high P waves as more or less indicative of auricular hypertrophy. In measuring the height of this wave we have considered the P-T, and disregarded the P-R, ratio. The T wave is normally higher than the P, i e, the P-T ratio is normally less than one. And so in cases in which the T waves were of normal average height, and the P-T ratio equal to or greater than one in one or more derivations, the curve has been considered suggestive of auricular hypertrophy—increasingly so as more derivations were involved. When the T wave was inverted, actual changes in the P height have been used as criteria, and a P wave which to the eye was plainly higher than normal has been considered suggestive of auricular hypertrophy. When both P and T waves were very small and much below the normal size, a P-R ratio of more than one has not been held to mean hypertrophy, i e, we have felt that

* Submitted for publication May 24, 1915

† From the Medical Clinic of the Johns Hopkins University

1 Einthoven, W. Le Telecardiogramme, Arch internat de physiol, 1906-7, 11, 148

2 Kraus, F, and Nicolai, G F. Ueber das Elektrokardiogramm unter normalen und pathologischen Verhältnissen, Berl klin Wchnschr, 1907, xlv, 812

3 Samjolloff A. Ueber die Vorhoferhebung des Elektrokardiogramms bei Mitralstenose. München med Wchnschr, 1909, li, 1943

hypertrophy should be considered only in those cases in which there was an actual as well as a proportional increase in the P height

By way of checking up the relationship between the P wave and auricular hypertrophy, the electrocardiograms of thirty-seven cases of clinical mitral disease on file at this station were examined, in which auricular hypertrophy might reasonably have been expected. These included twenty of insufficiency only, fourteen of combined

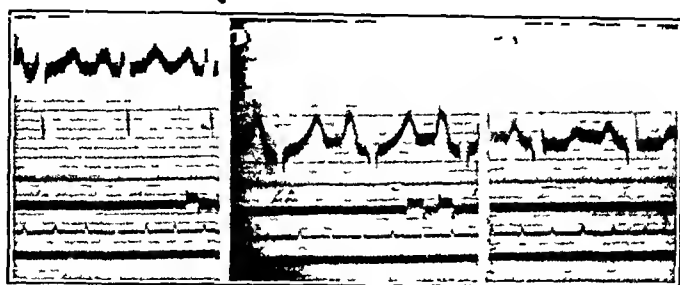


Fig 1—Case of mitral stenosis showing increase in height of P wave

stenosis and insufficiency, and three of stenosis alone. The curves showed marked relative or actual exaggeration of the height of the P wave in twelve cases, or 33 per cent. It was moderately exaggerated in eight more, uncertainly exaggerated in five, and definitely small in the other twelve. Thus there was some relative increase in height in 54 per cent of the cases studied. An example of the first group is shown in Figure 1, the electrocardiogram of R. K., white, aged 28. The diagnosis in her case was mitral stenosis and exophthalmic goiter.

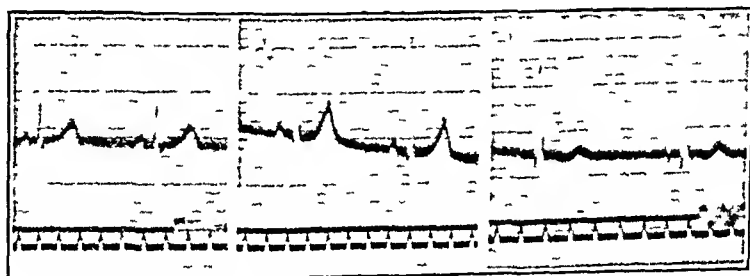


Fig 2—Case of mitral stenosis showing no increase in height of P wave

Her heart measured, to percussion, 10 cm. to the left and 4 cm. to the right in the fifth and fourth interspaces, and the patient showed the typical signs of mitral stenosis. This is the type of case from which a diagnosis of auricular hypertrophy would be made unhesitatingly if a high P wave be taken as pathognomonic of this condition.

On the other hand, Figure 2 shows the electrocardiogram of a typical case of mitral disease in which there is no increase in the height of the P wave. The patient, F. S., white, aged 14, had a clinical

diagnosis of mitral stenosis and insufficiency and aortic insufficiency His relative cardiac dulness measured 10 x 5.5 cm in the fifth inter-space He had been admitted eight years previously with a diagnosis of chorea and mitral stenosis, so his cardiac changes were of long standing, and auricular hypertrophy to be expected Yet the P wave is of normal size

Five cases of the above series came to necropsy Four of these showed auricular hypertrophy of varying degrees, the fifth slight dilatation of the right auricle only This last and one other showed no increase in the size of the P wave, in the other three there was some increase, but this did not vary directly with the hypertrophy Thus, one case of very slight hypertrophy showed a marked exaggeration of the P height, and one with much more marked hypertrophy a very slight exaggeration It is to be noted that the only case in which the auricles were found tremendously dilated and hypertrophied, the mitral narrowing being very marked, was that of F G, colored,

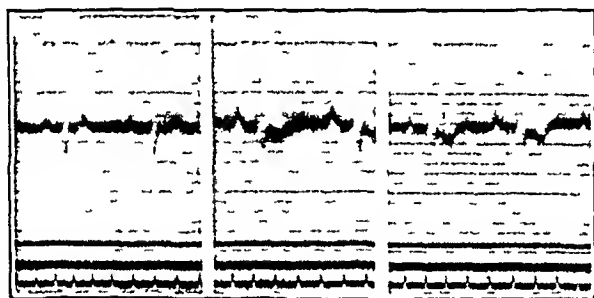


Fig 3—Case which showed at autopsy very marked dilatation and hypertrophy of the auricles P wave increased in height in D_2 only

aged 26, whose electrocardiogram is shown in Figure 3 It was taken three and a half months before death, the diagnosis being mitral stenosis and insufficiency A high grade of auricular hypertrophy was probably then extant, as the cardiac symptoms were of three years' standing, yet, except for a relative enlargement in D_2 the height of the P wave is not increased, and its appearance would not suggest more than slight hypertrophy It is noteworthy that the jugular tracings in this case showed a huge auricular "a" wave

The matter was approached from another standpoint, and forty cases of electrocardiograms with high P waves were discovered in some seven hundred cases on file The histories of the patients comprising this list were then examined In four instances, the patients not being hospital cases, no history was available Of the other thirty-six, sixteen, or 45 per cent, had a diagnosis of mitral disease Thirteen others showed myocardial insufficiency, associated with syphilis, myocarditis, or chronic nephritis, auricular hypertrophy being a reasonable presumption There were two cases of paroxysmal tachycardia, one

of pulmonary tuberculosis with positive Wassermann test, two of hyperthyroidism, one with an associated pulmonary tuberculosis, and two of psychoneurosis, one with a positive Calmette test and one uncomplicated

The electrocardiogram of this last is shown in Figure 4. The patient, Mrs. C., housewife, had suffered from nervousness, "dazed condition," and chronic constipation since the birth of her first and only child six years previously. Examination showed a normal woman with normal cardiovascular findings and a rather small heart. Her relative cardiac dulness measured 7×3.5 cm. in the fifth interspace. The electrocardiogram shows relatively large P waves in all derivations, and might readily be diagnosed one of auricular hypertrophy.

A study of the foregoing figures is conducive to the belief that although mitral disease with presumptive concomitant auricular hypertrophy and large P waves are associated in a considerable percentage of cases, this association is not a constant one. And it would seem

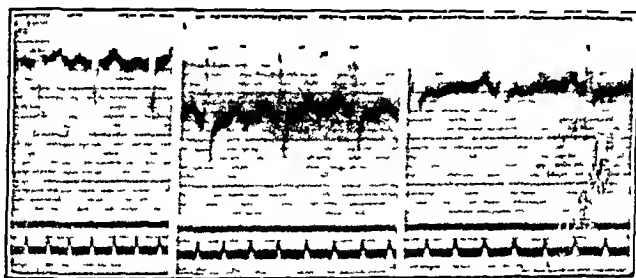


Fig. 4—Case with clinically normal heart showing increase in height of P wave

that while auricular hypertrophy probably in many instances exerts a causative influence, there must be many other factors which modify the height of the P wave. Indeed Einthoven⁴ has demonstrated experimentally that increase in the height of this wave may be produced by cutting the vagus in dogs. He reports that vagal section may be followed by a rise in the P wave to nearly three times its former height. Plainly no gross organic change can take place in the auricles during the course of such an experiment, and we must look for other factors to explain the results recorded.

Changes in the height of the P wave may occur from beat to beat, as Figure 5, the electrocardiogram of a case of complete heart block of luetic origin, shows. The auricular wave immediately following a ventricular systole is comparatively small but there is a progressive increase in the height of the P waves until the next ventricular response occurs, when the cycle is repeated. It might be suggested

⁴ Einthoven, W. Weiteres über das Elektrokardiogramm, Arch f d ges Physiol, 1908, cxvii, 537

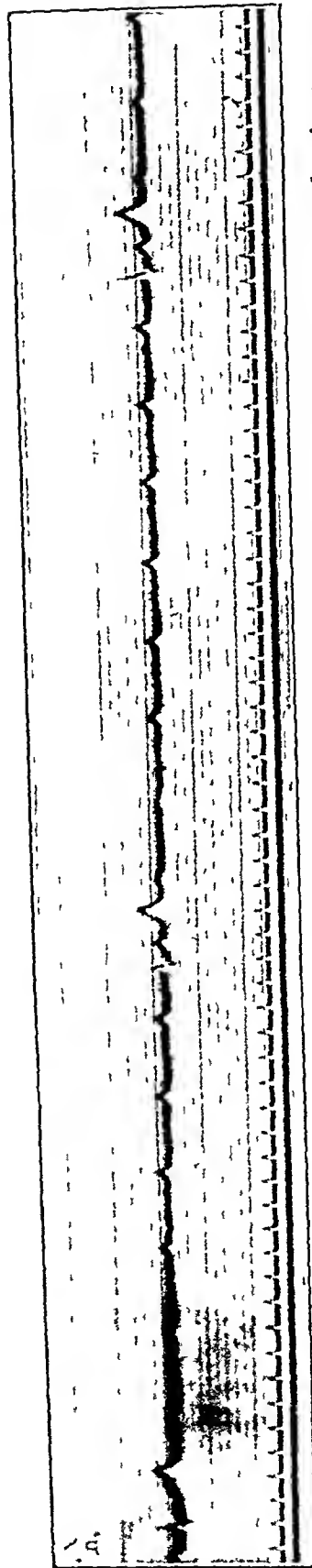


Fig 5—Complete heart block — luetic origin Progressive increase in height of P waves between ventricular beats

that each succeeding beat of the auricles, between ventricular beats, was working against greater pressure than the one immediately preceding, and that slight but progressively increasing functional dilatation was thus produced, such pressure and dilatation being relieved when the ventricle finally contracted. The idea of auricular dilatation exaggerating the height of the P wave is rather a novel one, and not well supported in the electrocardiographic findings in the two cases of our series which showed auricular dilatation at necropsy.

A review of the above findings would incline one to the belief that whatever the association between high P waves, mitral disease, and auricular hypertrophy, the dogmatic assertion that all cases of mitral stenosis will show high P waves, or that all cases of high P waves mean auricular hypertrophy, would be open to grave chance of error.

In reviewing the P waves of the seven hundred cases mentioned, the fact at once became apparent that inversion of this wave scarcely ever occurred except in the third derivation.

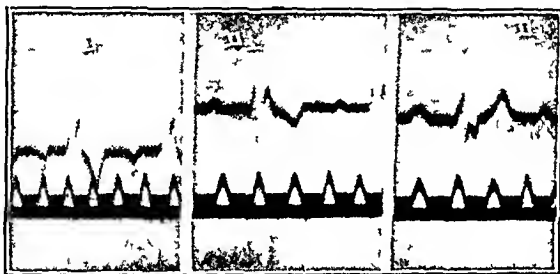


Fig 6—Same case as Figure 5, with normal sequence reestablished. P wave inverted in D_1 , upright in D_2 and D_3 .

It seems advisable to link inverted and diphasic P waves under one head, and, for simplicity, to speak of them all as "inverted," except where there is reason for differentiation. For the causative agents are apparently the same in both cases, and it is often difficult to classify a wave strictly under either heading. This is due to the fact that it may vary in appearance at different periods in the same curve, being now definitely inverted, now plainly diphasic.

To be specific, the P wave was inverted in the first derivation in but four cases of the entire series. Three of these were cases of *situs inversus*, in which such a phenomenon was to be expected. The fourth was the case of luetic heart block already referred to. The block passed off under treatment, and in an electrocardiogram taken later all waves were inverted in D_1 , as in *situs inversus*. The relations in the second and third derivations, however, differed from those found in *situs inversus*. At this time the conduction time was prolonged (Fig 6). Excepting the cases of *situs inversus*, this is the only case in which we have seen inversion of the P wave in D_1 without

inversion in the other two derivations. Of additional interest is the fact that the electrocardiogram of this patient while in a state of complete block showed a normal upright P_1 and P_2 with a diphasic P_3 (Fig 7), while a subsequent tracing, of later date than Figure 6, has shown upright P waves in all derivations (Fig 8). It is clear from this that changes in the direction of the P wave are not necessarily constant when once observed in a given patient.

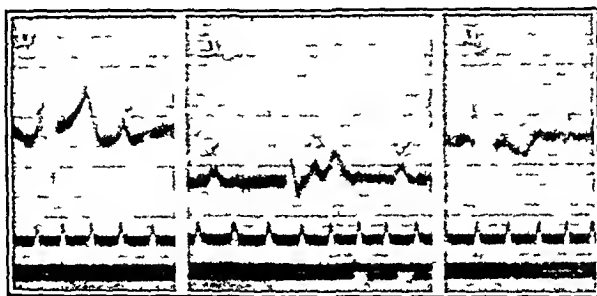


Fig 7—Same case as Figures 5 and 6. Complete block. P wave upright in D_1 and D_2 , diphasic in D_3 .

In a single instance, the P wave was diphasic in all derivations. The patient, R S, colored, 35, was admitted in great decompensation with a right hydrothorax and a relative cardiac dulness extending 17 cm to the left in the sixth interspace. The Roentgen ray showed a large heart lying transversely, with an unexplained mass (aneurysm?) in the region of the right heart. Diagnosis was myocardial insufficiency, arteriosclerosis, chronic nephritis. He was discharged improved with a relative cardiac dulness of 13 x 5 cm in the fifth and fourth interspaces.

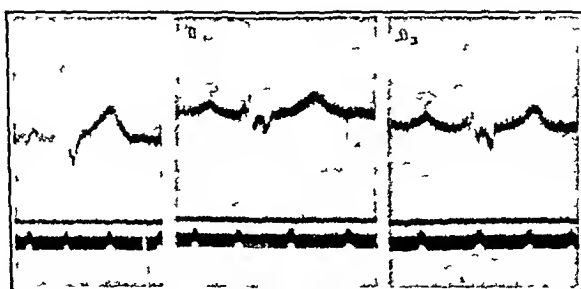


Fig 8—Same case as Figures 5, 6 and 7. Block has disappeared. P wave upright in all derivations.

The P wave was diphasic or inverted seven times in D_2 , in patients with varying clinical diagnoses. In all of these it was inverted in D_3 also. In one case, R Z, white, 23, no cardiac lesion was made out, the diagnosis being neurasthenia. The heart was enlarged, however, the relative cardiac dulness measuring 11.5 x 4.5 cm. In this instance the P wave varied in cycles, being upright, then diphasic, then inverted,

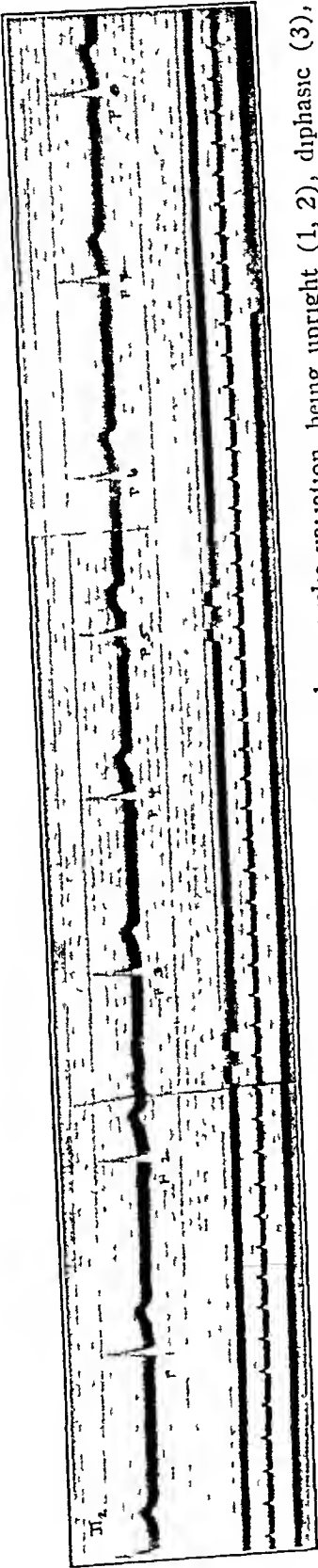


Fig 9—Case of neurasthemia with clinically large heart P wave shows cyclic variation, being upright (1, 2), diphasic (3), inverted (4, 5, 6), diphasic (7), and finally upright again (8)

then diphasic, and finally upright again (D_2) The duration of a cycle was too long to ascribe it to respiratory effect The electrocardiogram showed a pulse rate of 50, P_2 as described, diphasic P_3 and split R_3 , otherwise normal (Fig 9)

In seventy-five cases, about 11 per cent of all on file, P_3 was diphasic or inverted It is to be remembered that all cases of such changes in D_1 and D_2 numbered together but twelve Examination of the clinical histories naturally showed that heart lesions were present in the majority of instances, since it is not the practice here to take electrocardiograms of many cases outside the cardiac type Nevertheless, several cases were available in which diagnoses such as "chronic appendicitis and enteroptosis," "hyperthyroidism," "psychoneurosis and neurasthenia," "atrophic cirrhosis of the liver, pellagra," were made, and in which the cardiac condition seemed normal, although in most of these a large relative cardiac dulness, suggestive of emphysema or pulmonary tuberculosis, made auricular changes possible At least

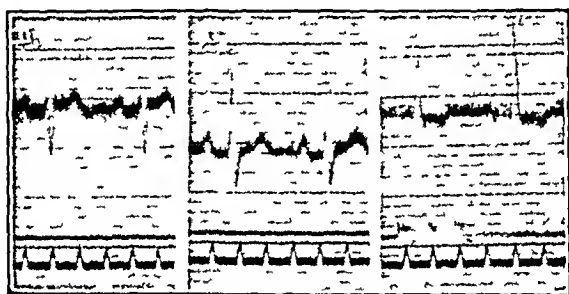


Fig 10—Case with clinically normal heart showing inverted P wave in D_2

three cases, however, appear to be above suspicion The first was N U, white, a neurotic girl of 16, with a diagnosis of hyperthyroidism, and a normal heart The second (Fig 10) was a case of periodical paralysis in a young man of 23 with a relative cardiac dulness of 9×4.5 cm, and a clinically normal heart The third, M T, white, aged 54, was a case of chronic cholelithiasis following typhoid fever His relative cardiac dulness measured 8.5×4 cm in the fifth and fourth interspaces Following operation he died of hemorrhage Autopsy showed normal auricles

Another case that came to autopsy should be noted The patient, T S, colored, aged 65, had had cardiac symptoms for a year and a half The diagnosis was syphilis, mitral insufficiency, and chronic nephritis The electrocardiogram, taken two weeks before death, showed beautiful inversion of P_1 and P_3 At autopsy the right auricle was slightly dilated, the left normal

Seven of the thirty-seven mitral cases previously referred to showed inverted P_3 In only *one* of these was there any relative

enlargement of the P wave This was in P J, a woman of 20, diagnosis, mitral stenosis There was progressive increase in the height of the R wave, the so-called "Right ventricular hypertrophy sequence"

An interesting feature was the discovery that 70 per cent of all cases of inverted P wave showed the "left ventricular hypertrophy sequence," a progressive decrease in the R and increase in the S wave These figures are not quite so impressive when we know that 47 per cent of all the cases on file showed this sequence, but still they remain very significant Twice only was the right ventricular hypertrophy sequence present One of these cases was in P J, referred to in the paragraph preceding The other was that of a child of 8 years with a diagnosis of mitral stenosis and insufficiency, and aortic insufficiency

It is worthy of note that in almost every instance in which neither ventricular sequence was present, interesting changes in the Q and S waves took place, i e, a progressive increase or decrease in the size of one or both

As to the causes of inverted P waves, their marked tendency to appear only in D₃, and their association with the left ventricular sequence, one can but speculate Consideration of the facts at hand would lead to the impression that actual organic changes in the auricles are by no means necessary factors in the causation of the inverted P Age may have an effect, only three of our series occurred in children (all with diseased hearts), but then the percentage of children's electrocardiograms on file is very small It would seem, however, judging from the association between the inverted P and the left ventricular sequence, that the former, as the latter, will tend to appear more frequently with advancing age The left ventricular sequence appears to be rather a normal finding in persons past middle life, i e, it can hardly be considered necessarily indicative of pathological conditions, as Bridgman⁵ has suggested Similarly, although the inverted P is a less frequent finding, it would appear that it will tend to be found normally in a certain percentage of healthy adults

Einthoven⁶ has demonstrated that vagal stimulation may so reduce the height of the P wave that it becomes diphasic Why then may not other influences not at present recognized produce similar changes, the auricles remaining uninjured? Perhaps vagal effects have some part in the clinical findings as well as the experimental, but hardly a prominent one, for vagotomie was not a feature of the cases studied Pulse rates varied between wide limits, as did blood pressure Cardiac position and respiratory influence may well each play a part Other, probably more important, factors remain to be determined

5 Bridgman, E W The Value of the Electrocardiogram in the Diagnosis of Cardiac Hypertrophy, *THE ARCHIVES INT MED*, 1915, xv, 487

6 Einthoven, W Weiteres uber das Elektrokardiogramm, *Arch f d ges Physiol*, 1908, cxii, 540

CONCLUSIONS

1 Although mitral disease, with presumptive auricular hypertrophy, was accompanied in 54 per cent of our cases by some relative increase in the size of the P wave, cases occur in which no such increase is found, and autopsy may reveal marked auricular hypertrophy which the electrocardiogram hardly suggested

2 A considerable number, 45 per cent in our series, of large P waves are associated with mitral disease, but such waves also occur in other conditions and in persons with clinically normal cardiac findings

3 Inversion of the P wave is commonly found in D₃ only, in 70 per cent of these cases in our series the phenomenon was associated with the "Left ventricular hypertrophy sequence"

4 Inverted P waves occur at all ages The size and shape of the P wave may vary at different periods in the same curve, and an inverted P in one record may appear upright in a later tracing, and vice versa

The causative factors in inversion of the P wave are yet to be determined

I am indebted to Dr E W Bridgman for many of my case records and other generous assistance

SEVERE ANEMIA WITH REMARKABLE ELONGATED AND SICKLE-SHAPED RED BLOOD CELLS AND CHRONIC LEG ULCER

JEROME E COOK, M.D., AND JEROME MEYER, M.D.
ST LOUIS

The unusual character of the blood findings in the case here recorded is alone sufficient to justify its report. When, however, we compare these findings, as well as the clinical history, with two similar cases previously reported, one by James B. Herrick, the other by R. E. Washburn, we are forced to the conclusion that we have in these three cases a group which belongs quite apart from anything heretofore described. We desire to present the history and findings in our own case, with the abstracts of the cases of Herrick and Washburn, and to show that the three have points of resemblance so characteristic and so constant that they cannot be explained as accidental. Our thanks are due to the above-mentioned authors for the opportunity of examining blood smears of their cases and for other courtesies.

AUTHORS' CASE—*Personal History*—O. B., a mulatto woman, aged 21, entered the Washington University Hospital, Nov. 3, 1914, giving the following history. She was born in St. Louis and had never been out of its immediate vicinity. She had had most of the diseases of childhood, and suffered at intervals, ever since she could remember, with "rheumatic" pains, the joints had never been swollen. Shortly after her marriage two years ago, she developed "pus-tubes," which were removed a year later. At the age of 5 an ulcer broke out on her ankle, which healed in about a month, under treatment. This did not recur until two years ago when a similar condition developed which lasted three or four months and was healed with scarlet-red ointment and bichlorid packs. Ten months before entering the hospital the ulcer again appeared. It caused her no pain and has been treated in various ways.

Physical Examination—Nov. 3, 1914. The patient was a light colored mulatto, with evidence of some loss of weight, conjunctivae and mucous membranes rather pale. The conjunctivae had a greenish tint. The rest of the physical examination, with the exception of the leg condition to be described, was not significant. There was a soft systolic murmur at the apex, transmitted to the left axilla, and heard over the left precordial area, the second pulmonic was louder than the second aortic and definitely accentuated. The systolic blood pressure varied from 105 to 125, the diastolic between 60 and 65. The lungs were clear, the spleen not palpable. On the left ankle, just above the internal malleolus was an ulcer 3 by 2 cm., the edges slightly indurated, the whole being of a light pink color. On the outer side of the ankle there was a scar 7 cm. by 3 cm. The skin in this region was dark and shiny.

Submitted for publication June 17, 1915.

From the Department of Internal Medicine, Washington University Medical School.

Course—The ulcer soon healed under bichlorid dressings, has remained closed since, and now presents a smooth, irregular surface, not depressed, of rather glossy and somewhat transparent texture, not white, but rather of an ivory color through which a fairly close network of capillaries can be discovered on close examination. Since her discharge from the hospital, Dec 3, 1914, the patient has gained in weight, feels stronger, and looks in every way improved. Our principal interest has, from the first, been centered on the blood picture. This will be taken up in detail later. Its unusual character made us feel that a full knowledge of the patient's family history possessed more than ordinary importance. We were able, by consulting several sources, to obtain fairly complete and accurate data.

Family History—Patient's father, A W, a mulatto, aged 54, has no knowledge of any blood relation except his children. The patient's mother died six years ago, aged 51, of breast cancer, twenty months after the disease was first noticed. The patient is the youngest of four children, there having been two boys and another girl. The first boy died at the age of 7. Up to a year before his death he was well nourished and apparently well, he then grew thin and sallow, had no cough, became progressively thinner, but was only confined to bed ten days before his death. The next child, a girl, died at the age of 22, of tuberculosis. She was healthy up to her fifth year, after which she became thin and sallow and suffered with pains in the extremities. The next child, a boy, died nine years ago at the age of 17. He was seen by Dr E W Saunders, who furnishes the following note of the family at that time. "I found the children the victims of severe anemia. One of them died and then I lost sight of the family." The father says that this boy was strong and fat up to the age of 6, after which he began to get weak and very pale. None of the children except our patient had leg ulcer. The patient's mother was born in St Louis and was never outside of the city. She was a healthy woman up to the time of her last illness. The mother's family history reveals nothing significant, with the exception that there seems to have been a large admixture of white blood. The mother's sister and her daughter are living in St Louis. They are light colored mulattos whose general appearance bear out the statement that they are in good health. Owing to some family enmity we have, as yet been unable to persuade these two to submit to nearer examination nor even to permit blood smears to be taken.

During the patient's stay in the hospital numerous blood examinations were made. The most striking feature was the shape of the red cells in the fresh and stained preparations. The illustrations show the condition in general, though there are many variations in each type.

Many of the red cells, about one in three, on rough count, were elongated, oat-shaped or crescent-shaped, with the same color and structure as the normal red blood cells. Some of the crescent-shaped cells in the fresh drop would curl and bend as if they were unusually pliable. There was considerable variation in the size of the red cells and also many structures which seemed to be fragments of cells, as if some of the cells had been crushed. The rather uniform character of these fragments, however, suggests that they were not artefacts. Nucleated reds were always present and at times were quite numerous. With Romanowsky stains there was only slight polychromatophilia.

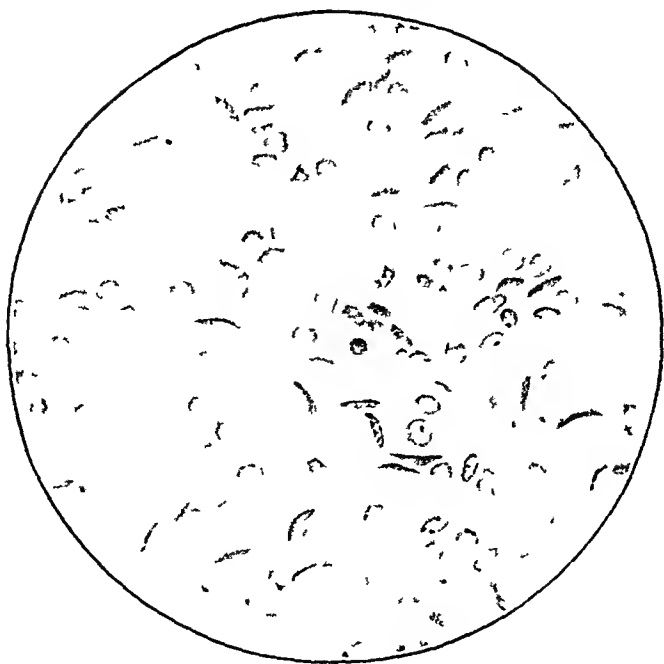


Figure 1

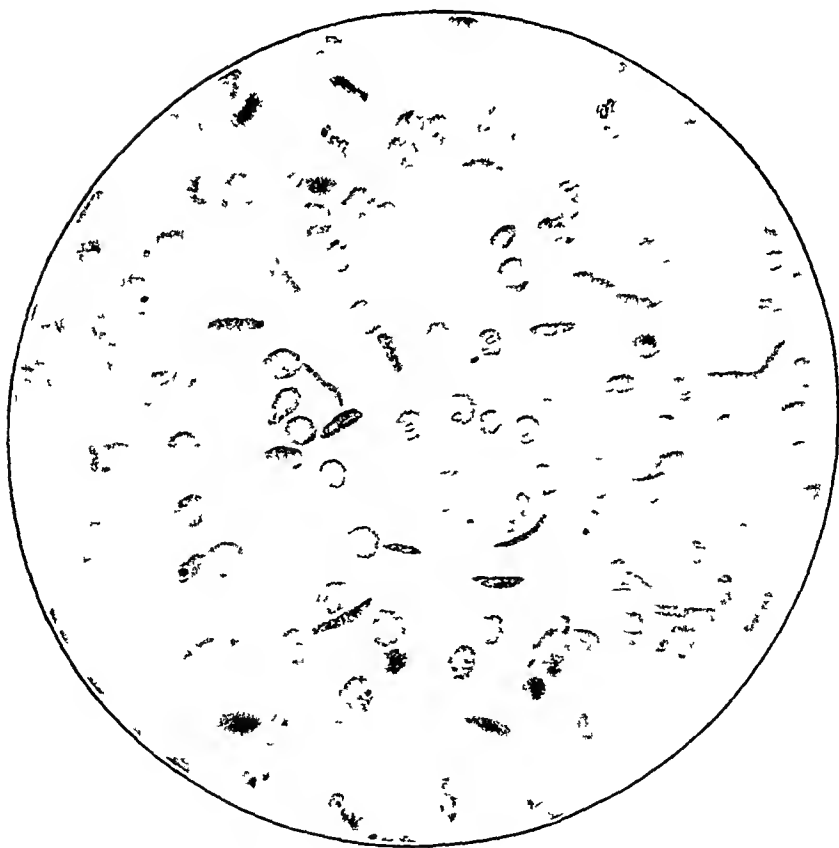


Figure 2

Figs 1 and 2—Elongated and sickle-shaped red blood cells

The red cells varied in number between 1,800,000 and 3,100,000, usually about 2,500,000, there was at all times a leukocytosis of mild degree, the color index averaged slightly below 1, and there was a constant eosinophilia at the expense of the polymorphonuclear cells. The following counts show the variations and are selected from a large number, made at short intervals

CELL COUNT AND HEMOGLOBIN

Date	Red Blood Cells	White Blood Cells	Hemoglobin, %
11/ 3/14	2,008,000	10,560	43
11/10/14	2,240,000	10,320	45
1/14/15	2,960,000	14,200	53

DIFFERENTIAL COUNTS

Date	No of Cells Counted	Normoblasts	Intermediates	Lymphocyte, %	Large Mononuclear, %	Polymorphonuclear, %	Eosinophil, %	Basophil, %
11/ 5/14	1,000	21	11	17.8	10.6	58.4	12.6	0.6
11/14/14	200	4	1	30.5	9	37.5	26	3
1/10/15	200	8		23	8	55	12	2

Before entering the Washington University Hospital, the patient had been in the Skin and Cancer Hospital. The blood examinations, made by Miss Florence Miller, clinical pathologist, show that the condition of the blood was about the same as in our experience. During the patient's stay in this institution search was also made for blood parasites, but without result.

The eosinophilia was subject to constant variation of rather wide range, and at one time we were able to follow a rise in the count from 3 per cent to 26 per cent within eleven days. The intense eosinophilia awakened the suspicion that the patient harbored a parasite. The stools were very thoroughly searched for evidence of this, but without avail. Nor did repeated examinations of the blood taken at all periods of the twenty-four hours, including centrifuged preparations of the citrated blood, reveal anything which could be interpreted as parasite or ovum. The Wassermann reaction was negative and an injection of salvarsan had no effect on the blood picture or the leg ulcer.

The suggestion that the abnormal shapes are artificial cannot well be proved. Some of the differences in shape depend on position, as

can be seen by watching a fresh preparation, but we could never see the change from oval or oat-shaped bodies to worm-like or sickle-shaped, or the reverse. We could not avoid getting the same forms, no matter how carefully the preparations were made, nor could we produce similar changes in normal or anemic blood from other cases. Dr V E Emmel, associate professor of anatomy, who has made extensive studies of blood development and morphology, was much interested in this feature of our case, and made many investigations into possible explanations. His results will be published later.

The possibility of an inherited anomaly suggested itself. The fact that the three other children of the family had suffered from severe anemia encouraged investigation in this direction. Examination of the father's blood showed 4,500,000 red cells, 11,100 white cells, and 86 per cent hemoglobin. Differential count showed polymorphonuclears 68 per cent, lymphocytes 20 per cent, large mononuclears 8 per cent, eosinophils 4 per cent. The stained smear showed none of the peculiarities of the daughter's blood. Dr Emmel, however, found some resemblance in the behavior of the blood. When preparations of the fresh blood were sealed under precautions which insured sterility and allowed to stand for several days at room temperature, the microscope revealed long, sharp projections and elongations from many of the red cells in the blood of both the father and the daughter. Dr Emmel has not found similar appearances in the blood of any other person.

The following case was reported by Washburn ¹

WASHBURN'S CASE—The patient had been under observation since 1907, a negress, aged 25, a native and resident of Southwest Virginia all of her life. When admitted to the University of Virginia Hospital in 1910 she complained of weakness, soreness and pain in the left side, and a sore on left leg. When a child she had pneumonia and within the last five years has had chills and fever, supposedly malaria. On admission she had shortness of breath on exertion, night sweats and swelling about the wrists and ankles. There were occasional attacks of abdominal pain and indigestion.

The patient's father, an old man, has been in bad health for many years. The mother died twenty years before. The patient had four brothers, all of whom died while small, and four sisters, three of whom died in childhood, while one died recently of some brain trouble. The patient's illness dates back five years, when she noticed some dizziness, shortness of breath on exertion, and swelling about the wrists and ankles. At the same time she knocked some skin off the left shin, resulting in an ulcer. Some time later an ulcer started on her right leg, though she remembered no injury. The patient was operated on for gall stones in 1908. In April, 1909, the following blood examination was recorded: Red cells 2,000,000, white cells, 11,000, hemoglobin (Sahli) 50 per cent. Differential white count was as follows: Polymorphonuclear 63 per cent, small mononuclear 25 per cent, large mononuclear 2 per cent, eosinophil

¹ Washburn, R E. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia, *Virginia Med Semi-Monthly*, 1911, vi, 490

4 per cent, mast cells 6 per cent The red cells showed poikilocytes in a variety of shapes, the most common being of a crescent shape Washburn sums up his case as follows

The case is one of severe anemia, characterized by a peculiar poikilocytosis, oligocythemia and a color index less than one, together with nucleated red corpuscles, myelocytes and an increase in the percentage of eosinophils Among the suspected causes were syphilis and intestinal parasites, but both of these seem to be disproved There is no definite history of syphilis, and the iodids, though given until the physiological effect was produced, had no apparent influence on the anemia or on the leg ulcers No intestinal parasites capable of producing the trouble were found on examination of the stools either before or after the administration of thymol The facts do not seem to warrant diagnosis as to the cause of the condition

The following is abstracted from the case of James B Herrick²

HERRICK'S CASE—The patient, a negro of 20, had been in the United States three months, his former residence was in the West Indies, where he was born He was one of four children, all the others being healthy At the age of 10 the patient had had yaws, which was common in his locality The disease lasted about one year and was characterized by ulcers on the legs, described as pustular with scabs, the scars of which remained For about a year previous to coming under Herrick's observation he had noticed some palpitation and shortness of breath, and for about three years had had a disinclination for exercise On landing in New York, September, 1904, he had a sore on one ankle which healed with tincture of iodine, leaving a scar similar to those on limbs The patient came to Herrick for treatment of a "cold" Physical examination showed a young man, well developed physically, a tinge of yellow in the sclera and pale mucous membranes The cervical, axillary, inguinal, and epitrochlear glands were definitely enlarged The scars to which he referred were nearly all located on the legs and thighs, perhaps twenty in all They were rounded or oval, sometimes of irregular contour, the edges clean cut, some were like tissue paper or thin parchment to the touch and were lighter in color than the surrounding skin They were strikingly like scars often seen as a result of syphilis A faint systolic murmur was heard over the base of the heart and to some extent over the apex The blood examination on Dec 26, 1904 was red cells 2,880,000, white cells, 15,250, hemoglobin 50 per cent Differential count, polynuclear 72 per cent, small mononuclear 15 per cent, large mononuclear 7 per cent, eosinophil 5 per cent Nucleated reds were common The shape of the red cells was very irregular, but what especially attracted attention was the large number of thin elongated sickle-shaped and crescent-shaped forms These were seen in fresh specimens no matter how the blood was spread on the slide, they were likewise always present in the fixed specimens Under treatment the blood improved in quality, but there was still a tendency to the peculiar crescent shapes in the red cells, though this was not so noticeable as before Nucleated reds were present Eosinophils made up 5 percent of the total white cells On March 7, 1906, a blood count was made that showed red cells 2,700,000 white cells 30,500, hemoglobin 55 per cent Differential count, polynuclear 58 per cent, small mononuclear 22 per cent, large mononuclear 12 per cent, eosinophil 7 per cent, myelocyte 1 per cent The elongated and spindle forms were numerous and there were many nucleated reds The patient passed from observation in 1907 in about the same state of health as before

Careful search of the literature has been made for other similar cases or for any blood picture resembling that of our case, but we

² Herrick James B THE ARCHIVES INT MED, 1910 vi 517

have discovered no text-book or article which refers to elongated and sickle-shaped cells such as we have described. A search of this kind must of necessity be incomplete, it adds some testimony, however, to the fact of the extreme rarity of this condition. The only accounts which we have found and which, though seemingly unlike our case, may have some relation to it and are for that reason mentioned here, have been published by Bishop³ and Dresbach⁴. The former reports a patient 70 per cent to 80 per cent of whose red blood cells showed "a more or less well marked elliptical outline". Most of the elliptical cells measured 13 by 5 microns. The red blood cells numbered 5,400,000, hemoglobin 110 per cent. The sister's blood showed the same condition of the cells and her red blood cells numbered 5,000,000 with 100 per cent hemoglobin. Four other members of the immediate family showed a normal blood picture. We are indebted to Dr. Bishop for the privilege of examining blood smears from his case. Dresbach reports a similar case in a mulatto, aged 22. There were 5,000,000 red blood cells, about 90 per cent of which were more or less oval. The greatest variation showed a minimum diameter of 3.9 microns, with a maximum of 10.7 microns. A brother had normal corpuscles. In both cases the general health was good with normal red and white counts and hemoglobin and an absence of nucleated red cells.

It will be seen that there is a striking similarity in both the blood picture and the clinical history of our case with those of Washburn and Herrick. All three of the patients were of negro blood, all three suffered from peculiar, indolent, recurring leg ulcer, in all three the anemia was sufficiently severe to cause dyspnea on exertion, and in all of the cases there was a peculiar discoloration of the sclerae, which in our case and that of Washburn is described as a "greenish tinge" and which Herrick notes as "a tinge of yellow", in no case could enlargement of the spleen be made out, responsibility for the condition could not be placed on syphilis or a parasite, although a careful examination was made in each case for such a possible etiological factor.

The uniformity of the blood abnormality is even more striking, the individual differences being of degree rather than of kind and depending no doubt to some extent upon the time at which observations were made.

The red cells in the three cases, in the numerous examinations made, varied between 1,800,000 and 3,000,000 with a striking tendency to remain around 2,500,000. In all of these cases there was a leuko-

3 Bishop F. Warner. Elliptical Human Erythrocytes, *THE ARCHIVES INT MED*, 1914, LIV, 383.

4 Dresbach, Melvin. *Science*, 1904, XI.

cytosis of more or less marked degree, and in all cases there was an eosinophilia of distinct but varying degree. A varying number of nucleated red cells was present in all cases, in no case were they rare or difficult to find. A glance at the blood slides leaves no doubt as to the identical character of the elongated and sickle-shaped red cells. The percentage of these cells was greater in our case than in the other two, but even in these it was considerable.

We wish to express our thanks to Dr. George Dock for the privilege of studying the case and for his suggestions in the preparation of our work.

A STUDY OF THE HEMOLYTIC ACTIVITY OF THE SPLEEN IN PERNICIOUS ANEMIA *

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There is a certain amount of evidence that the increased blood destruction occurring in pernicious anemia is in some way associated with an abnormal functioning of the spleen, since removal of this organ brings about a marked reduction in the quantity of blood destroyed. This reduction has been found in almost every instance where the blood destruction was studied before and after splenectomy.¹ Eppinger and Ranzi² and the author,³ who report the two largest series of cases, found that the greatly increased hemolysis present before operation showed a constant and marked decrease afterwards, reaching normal in all but two or three cases. Yet the manner in which the spleen acted to produce increased blood destruction is as yet undetermined.

The literature contains comparatively few observations on the hemolytic activity of the human spleen either in normal or pathological conditions. Benard⁴ tested salt solution extracts of two freshly excised normal human spleens and obtained negative results. In a case of severe hemolytic anemia with marked jaundice, Antonelli⁵ was unable to demonstrate any hemolytic activity with a saline extract of the freshly excised spleen. Port⁶ studied the spleen in one case of pernicious anemia immediately after operation, using both alcoholic and ethereal extracts. His results were entirely negative. McPhedran⁷ however, working with ethereal extracts, found a substance in the spleen obtained at postmortem from a case of pernicious anemia, which possessed a strong hemolytic action. This hemolysin, which belonged to the group of unsaturated fatty acids, could, however, be extracted from the liver and intestinal wall and was also found in normal organs other than the spleen.

* Submitted for publication June 8, 1915

^ From the Pathological Laboratory of the Massachusetts General Hospital

1 The quantitative estimation of urobilin in the stool was used as an index to the degree of blood destruction

2 Eppinger, H, and Ranzi, E. *Mitt a d Grenzgeb d Med u Chir* 1914 xxvii, 796

3 Robertson, O H. *THE ARCHIVES INT MED*, 1915 xvi 429

4 Benard, H. *These de Paris*, 1913

5 Antonelli. *Progressive Med*, June, 1914, p 327

6 Port, Fr. *Berl klin Wchnschr*, 1914, li, 546

7 McPhedran, W F. *Jour Exper Med*, 1913 xiii, 527

Several writers have suggested the possibility that the abnormal amount of hemolysis occurring in pernicious anemia may take place in the portal system, first on account of the lack of any evidence of hemolysis in the peripheral circulation, and second, because the chief deposit of iron is found in the liver. In a case of pernicious anemia with splenectomy, Eppinger⁸ tested the hemolytic properties of the blood obtained from the splenic vein at operation with a negative result. Huber⁹ in a similar case tested the resistance of the unwashed red blood cells from the splenic vein against hypotonic salt solutions. He found no difference between the splenic vein blood cells and the cells from the peripheral circulation.

In view of the few observations which have been made on this subject, it seemed desirable to record the results of a study of the freshly excised spleen and splenic vein blood in six cases of pernicious anemia recently in which the patients were operated on at the Massachusetts General Hospital for splenectomy.

SPLEEN

A histological study of the spleen in these cases was practically negative. There was no abnormal phagocytosis, no pigmentation, nor any other evidence of increased hemolysis.

The saline extract for the following experiments was made by adding to finely ground up fresh spleen pulp, twice its volume of normal salt solution. The mixture was then agitated in a mechanical shaker for one hour and finally centrifugated at high speed till no further sediment could be obtained. A very small quantity of red cells—0.05 c.c. of a 2 per cent suspension—was added to varying quantities of this extract, and after two hours at 37 C, the mixtures were centrifugated and read. There was no hemolysis either with the patients, or with normal cells.

Acting on the assumption that if conditions similar to those in the body were maintained, the result might be different, in the next case the spleen was kept warm and the process maintained at 37 C throughout. Under such conditions there was likewise no hemolysis. Benard stated in his experiments with dogs that he obtained a splenic extract actively hemolytic for the animal's own cells only when he perfused the spleen thoroughly with salt solution beforehand. Perfusion of the spleen in a third case made no difference, nor did keeping the extract for several days, which according to Widal, Abram and Brule¹⁰ tends to increase the hemolytic properties of the spleen extract.

⁸ Eppinger, H. *Berl klin Wchnschr*, 1913, 1, 2409.

⁹ Huber, O. R. C. *Berl klin Wchnschr*, 1913, 1, 2179.

¹⁰ Widal, Abram and Brule. *Bull Soc d hôp de Paris* 1912 No 13.

An alcoholic extract was next tried. This was prepared by shaking finely ground up spleen pulp with 95 per cent alcohol for several hours. The supernatant fluid was then decanted, evaporated to dryness, and the residue taken up with salt solution. This extract also failed to hemolyze red blood cells.

On account of Port's negative finding with the ethereal extract of a freshly excised pernicious anemia spleen, a portion of one spleen was extracted with ether. This extract showed an intensely hemolytic action, though not quite as strong as that found by McPhedran in the pernicious anemia spleen at postmortem. McPhedran's findings make it apparent that the extraction of the fatty hemolysins offers very little hope of differentiating the pernicious anemia spleen from the normal spleen.

This absence of any evidence of hemolytic activity characteristic of the pernicious anemia spleen, coincides with the negative histological findings. It is still possible that the spleen does possess a hemolysin, but that the methods used in attempting to extract it are unsuitable to demonstrate its presence.

SPLENIC VEIN BLOOD

Blood from the splenic vein was obtained at operation by aspiration into a syringe before the pedicle of the spleen was ligated. Owing to the difficulties in technic, the blood in two cases began to clot in the syringe, or so soon after drawing that it was not available for all the tests.

Hemolytic Properties—The plasma in the three cases in which the blood was obtained before clotting occurred, showed free hemoglobin, in two the plasma was definitely pink, in the third hemoglobin was evident spectroscopically. The presence of hemolysis here, however, can easily be accounted for as a result of manipulation during the delivery of the spleen from the abdominal cavity. Hemolytic experiments were made in two cases with the serum, using both the patient's own blood cells and normal cells, and as controls, serum taken from the patient's arm vein immediately before operation and serum from a normal person. Results were entirely negative and the addition of guinea-pig complement made no difference.

Morphology—Blood counts varied in their relations to those of the peripheral blood. One case showed a considerably increased number of red blood cells in the splenic vein, the other showed somewhat fewer. The white counts were both higher in the splenic vein, while the differential counts were practically identical with those of the peripheral blood. These variations from the peripheral blood cannot be relied on as representing actual differences, on account of the factor

of error due to the above mentioned manipulation, during which process a larger number of cellular elements than normal may have been squeezed into splenic vein

The appearance of the red blood cells was identical with that shown by the peripheral blood, with the exception that in one case there was a greater percentage of reticulated cells in the blood from the splenic vein. Blood platelets were strikingly abundant in spite of the fact that they were much diminished in the peripheral circulation. The fact that the spleen normally is a great storehouse for blood platelets, however, coupled with the factor of manipulation at operation, may well explain their great increase in the splenic vein at this time.

Resistance of the Red Blood Cells—The only positive finding which could not be explained as a result of operative procedure, was the decreased resistance of the red cells from the splenic vein. This was constant in the three cases tested. For controls the patient's blood taken immediately before operation and normal blood were used.

	Hemolysis Beginning at Pct Salt Sol	Hemolysis Complete at Pct Salt Sol
Case 1—Splenic vein blood	0.525	0.325
Peripheral blood	0.45	0.30
Control normal blood	0.45	0.325
Case 2—Splenic vein blood	0.675	0.325
Peripheral blood	0.425	0.30
Control—normal blood	0.425	0.325
Case 3—Splenic vein blood	0.675	0.35
Peripheral blood	0.525	0.35

In Case 2 the hemolysis, beginning at 0.675 per cent, was very faint and continued faint to 0.425 when it increased markedly. Case 3 showed well-marked hemolysis beginning at 0.675. In this case the blood was obtained from the spleen five to ten minutes after excision, which may account for a greater decrease in resistance than was shown by the other two cases. Huber's negative result might be accounted for by the fact that he did not wash the blood cells before testing their resistance, since unwashed cells are protected to a certain extent by the blood plasma present.

Banti¹¹ obtained blood from the splenic vein at operation in two cases, one a case of hemolytic splenomegaly and the other a splenic vein thrombosis. Both showed a decreased resistance of the cells from the splenic vein. Banti also compared the resistance of the splenic vein blood cells with that of the peripheral cells in dogs and found a slight but constant lowered resistance in the cells of the splenic vein. This difference in resistance was much increased after the

11 Banti. *Semaine med*, 1913, p. 313

injection of a hemolytic serum, suggesting that a possible normal function of the spleen had become markedly hyperactive. It seems not improbable that the decreased resistance found in the cells of the splenic vein in these cases of pernicious anemia, which was even greater than that in Banti's dogs, may have the same significance, *i. e.*, an evidence of injury received by the cells during their passage through the spleen due to some toxic substance elaborated by that organ. These injured cells would then be more easily broken down in other parts of the body. In this way the absence of any direct hemolytic action of the spleen could be accounted for.

It was thought possible that this change in resistance might be duplicated *in vitro* by allowing the cells to remain in contact with splenic extract. The patient's peripheral blood cells as well as normal cells were incubated for two hours with the saline extract, then washed and their resistance to salt solution tested. No change in resistance was observed. Neither were they less resistant to a hemolytic serum after this procedure.

SUMMARY AND CONCLUSIONS

1 In a study of the hemolytic activity of the fresh spleen obtained at operation, from six patients with pernicious anemia, it was found that extracts of the spleen pulp made with both normal salt solution and alcohol, possessed no hemolytic properties. An ethereal extract, on the other hand, showed a marked hemolytic action. However, the hemolytic substance contained in this extract belonged to the group of unsaturated fatty acids and has been obtained in equally strong concentration from the normal liver and intestine.

2 The only change in the splenic vein blood obtained at operation, which could not be accounted for by manipulation, was a decreased resistance of the red cells. These cells were definitely less resistant than those of the peripheral circulation in the same individual and in normal controls.

3 The above findings seem to exclude any gross or easily demonstrable manifestation of hemolytic activity on the part of the spleen. However, the decreased resistance of the red cells in the splenic vein, would suggest that the spleen in pernicious anemia elaborated some toxic substance or enzyme which so injures the blood cells during their passage through that organ that they are more susceptible than normally to destruction elsewhere. It seems probable that in some other part of the body there is elaborated an abnormal hemolysin or an abnormally acting normal hemolysin.

A BACTERIOLOGICAL AND CLINICAL STUDY OF THE NONTUBERCULOUS INFECTIONS OF THE RESPIRATORY TRACT, WITH SPECIAL REFERENCE TO SPUTUM CULTURES AS A MEANS OF DIAGNOSIS

PAPER I—INTRODUCTION, METHODS, GENERAL RESULTS OBTAINED, ORGANISMS FOUND AND THEIR RELATIONS TO THE VARIOUS INFECTIONS, AND A CONSIDERATION OF THE VALUE OF SPUTUM CULTURES *

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The present series of papers dealing with infections of the respiratory tract is not so much the product of a set problem, as an evolution of some work started four or five years ago. At that time, during an investigation to determine the comparative virulence of the pneumococcus in the sputum of lobar pneumonia at various stages of the disease, with special reference to crisis,¹ it became necessary to isolate the strains of pneumococci used, by means of sputum cultures on blood agar plates. I was then impressed with the ease with which this method could be used as a means of diagnosis in pulmonary infections other than pneumonia.

The first case under observation was that of a woman with acute bronchitis who had no previous history of cough or any disease pointing to an infection of the chest. The expectoration was typical, green, mucoid, and I was surprised on the next day to find a beautiful plate, consisting of a pure culture of green pneumococcus colonies. My conception of the pneumococcus was a narrow one. The pneumococcus in the chest to me meant pneumonia.

The next case was that of a robust middle-aged man, who had contracted a cold, following which he was suffering with severe fits of coughing occurring several times a day, at which times he would bring up fairly large, tenacious, green lumps of sputum. An examination of the chest showed marked impairment at the right base with

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* From the Medical Clinic of the Johns Hopkins Hospital

* Other papers in this series: Paper II—Acute and Chronic Bronchitis, Bronchopneumonia, and Lobarpneumonia, Paper III—Chronic Nontuberculous Infections of the Chest with Special Reference to the Pneumococcus, Paper IV—Acute Coryza, Acute and Chronic Sinusitis, Acute and Chronic Tonsillitis, Acute Laryngitis, Paper V—Whooping-Cough

¹ Luetscher, J. A. The Comparative Virulence of the Pneumococcus in the Sputum of Lobar Pneumonia at Various Stages of the Disease, with Special Reference to Crisis, Jour. Infect. Dis. 1911, 18, 287

modified tubular breathing and showers of râles. The Roentgen ray showed an infiltration of this area, with the diaphragm apparently hooked up as though by adhesions. The Roentgen ray diagnosis was tuberculosis. Tubercle bacilli were never found. This condition persisted for two months. The physical signs then cleared up, the Roentgen ray no longer showed any infiltration, and the diaphragm was in normal position. There had never been fever over 99°. During the entire illness the patient felt well, so well that he wanted to take his accustomed walks of miles in the country. The sputum cultures gave pure plates of typical pneumococcus colonies which could be isolated in pure cultures as long as the physical signs were present, and then disappeared. Here was another new conception for me, a local consolidation of a base, afebrile, with no toxic or constitutional symptoms lasting over a period of two months, caused by a typical pneumococcus.

The problem gradually evolved until in the past four years the whole respiratory tract has been investigated, including acute rhinitis, the accessory sinuses, acute tonsillitis, tonsils after enucleation, laryngitis, whooping-cough, bronchitis, bronchiectasis, the various pneumonias, atypical consolidations, and chronic infections.

While the other secretions and excretions of the body, such as urine, gastric secretions, and exudates are carefully examined chemically, microscopically and bacteriologically, the sputum has been practically neglected, with the exception of the search for tubercle bacilli. It is true that the sputum has been repeatedly cultured in the investigations of rare and isolated cases, also in series of cases of *suspected influenza epidemics*, but I have been unable to find any systematic study of a series of cases of lung infections, by means of sputum cultures other than those made by Lord,² Wollstein,³ Holt,⁴ and Hastings and Niles.⁵ Our knowledge of the respiratory infections is still drawn chiefly from necropsy findings, the results of which, owing to agonal and post-mortem invasions of organisms from the mouth and the intestinal tract, have been justly questioned.

2 Lord, F. T. Eleven Acute and Eighteen Chronic Cases of Influenza, *Boston Med and Surg Jour*, 1902, cxlvii, 662, *Infections of the Respiratory Tract with Influenza Bacilli and Other Organisms, Their Clinical and Pathological Similarity, and Confusion with Tuberculosis*, *Boston Med and Surg Jour*, 1905, cli, 537, 574.

3 Wollstein, M. The Influenza Bacillus in Inflammations of the Respiratory Tract in Infants, *Jour Exper Med*, 1906, viii, 681.

4 Holt, L. E. The Bacteriology of Acute Infections of the Respiratory Tract in Childhood, with Special Reference to Influenza, *THE ARCHIVES INT MED*, 1910, v, 449, *The Bacteriology of Acute Respiratory Infections in Children as Determined by Cultures from the Bronchial Secretions*, *Tr Assn Am Phys*, 1910, xxv, 223.

5 Hastings, T. W., and Niles, W. L. The Bacteriology of the Sputum in Common Nontuberculous Infections of the Upper and Lower Respiratory Tracts with Special Reference to Lobar and Bronchopneumonia, *Jour Exper Med*, 1911, xiii, 638.

A study of the results thus far obtained from necropsy material and sputum cultures will impress one at once with the great confusion and difference of opinion as to the etiological agent of the various respiratory infections. This is especially true of the infections of the upper part of the respiratory tract such as the nose, larynx, and bronchi.

The purpose of these papers is to demonstrate by means of sputum cultures an easy and reliable method of diagnosis of pulmonary infections, and to determine the etiological agent of these infections.

CAUSES OF INDIFFERENCE AND SKEPTICISM IN REGARD TO SPUTUM CULTURES

The usual conception of physicians in regard to sputum cultures is expressed about as follows: "You can't do anything with sputum cultures for you have such a mixture of organisms that you cannot tell whether one, all, or any of them bear any etiological relationship." Their idea is obtained from what they see on slides prepared and stained for tubercle bacilli, from sputum specimens indifferently collected and incubated at room temperature for hours, often days.

Then, too, the reports of the findings thus far have been so confusing that this opinion is rather strengthened. This is due to the character of mediums used. Anyone working with bacteriological problems of today knows that nearly all the work is done with special mediums, such as agar, broth or the various sugars enriched with fresh blood, blood serum, hydrocele fluid or the various exudates, all titrated accurately to a definite point for optimum growth, and that the ordinary laboratory medium is insufficient for the reason that organisms bearing an etiological relationship fail to grow or only so sparingly as to be overlooked or lost, and that only the ordinary contaminating organisms appear. It is only in recent years and by those working specially with influenza, that blood agar was used as a routine, and it is these workers who have obtained consistent results.

BACTERIA NORMALLY PRESENT IN THE RESPIRATORY TREE

Almost invariably, when one reports on the findings of a given respiratory infection, the question is asked as to the possibility of similar findings in normal cases.

Since the respiratory tree is an open channel, and since air may be laden with bacteria, one could readily assume that the lung is constantly inhabited by bacteria the same as the intestinal tract.

While we know that the air of high altitudes and at sea may be sterile, it has also been shown that the air of cities is laden with bacteria. One need only refer to the work of Hesse,⁶ who found 350

⁶ Hesse, W. Ueber quantitative Bestimmung der in der Luft enthaltenen Mikroorganismen, *Arb a d k Gsndhtsamte*, 1884, 11, 182.

organisms per ten liters of air in schoolrooms after dismissal, of Newman⁷ and Miguel,⁷ who found respectively 140 and 790 bacteria per ten liters in hospital wards, of Haldane,⁷ who found 8,500 bacteria per ten liters in a ropemaker's workroom, of Thomson and Hewlett,⁸ who found 164 organisms per ten liters in the thoroughfares of London, and of Sedgwick and Rockwell,⁹ who found 200,000 organisms per ten liters in a dust storm 5 feet above the surface of a macadamized road

The average amount of tidal air entering the lung being 500 cc and the average respirations per minute being about 18, the amount of air entering the respiratory tree is over 500 liters per hour. From these figures it can easily be deduced that one may inhale every hour 3,200 bacteria in the streets of London, 7,000 to 39,000 per hour in hospital wards, and 10,000,000 per hour in a dust storm on a highway.

It is therefore no surprise that most people have the conception of Rohrer,¹⁰ who states that it is *selbstverständlich* that the nose and nasopharynx must show a large number of fungi, besides bacilli and cocci. This view has also been expressed more recently in an editorial¹¹ in the *British Medical Journal* under the caption "To Blow or Wash" in which the writer expresses the opinion that the civilized nose is one of the dirtiest organs of the body.

In a very modern text Ewart¹² assumes that the bronchi are inhabited by an "exceedingly varied flora" and are apt to contain any of the organisms present in the air, in the nasal cavities and accessory sinuses, the tonsils and the pharynx, together with the *Aspergillus fumigatus*, *Oidium albicans* and other samples of lower vegetation, and also mentions the colon bacillus, the Friedlander bacillus, Löffler's bacillus, *Micrococcus tetragenus*, staphylococcus and others as among the "ordinary tenants" of the bronchi.

Because of these common beliefs, it seems desirable to bring in brief review the experimental facts.

BACTERIA PRESENT IN THE NORMAL NOSE

The nose and larynx have been cultured directly. Thomson and Hewlett,⁸ Park and Wright,¹³ Lewis and Turner¹⁴ found that the

- 7 Hygiene and Public Health, Whitelegge and Newman, p 7
- 8 Thomson, St Clair, and Hewlett, R T Micro-Organisms in the Healthy-Nose, Med-Chir Tr, Lond, 1895, lxxviii, 238
- 9 Sedgwick, W Principles of Sanitary Science and the Public Health, 1902, p 113
- 10 Rohrer Ref in Centralbl f Bakt, 1888, iii
- 11 Editorial Brit Med Jour, 1895, i, 213
- 12 Ewart, W System of Medicine, Allbutt & Rolleston, Ed 2, 1909, v, 79
- 13 Park, W H, and Wright, J Nasal Bacteria in Health, New York Med Jour, 1898, lxxvii, 178
- 14 Lewis, C J, and Turner, A L Suppuration in the Accessory Sinuses of the Nose. A Bacteriologic and Clinical Research Edinburgh Med Jour, 1905, xliii, 393

healthy nose contains so few bacteria that if one rubs the septum and turbinates with a sterile platinum loop and inoculates this loopful of mucus on the surface of a blood agar plate 75 to 83 per cent show no growth

Ten cultures made by myself in this manner from hospital physicians and students showed 50 per cent to be sterile, the other 50 per cent showing only 1 to 5 colonies, all of which were nonpathogenic

Surgical operations on the nose confirm the foregoing findings, since it is common knowledge that these wounds heal without sepsis

Thomson and Hewlett made some experiments on the fate of organisms entering the nose. They placed a loopful of *Bacillus prodigiosus* on a spot of the turbinates. Cultures made from this spot up to two hours showed the following

5 minutes, numerous
15 minutes, much less
60 minutes, diminished by 75 per cent
80 minutes, frequently no bacteria
2 hours, no bacteria could be found

This experiment shows that the nose rapidly cleanses itself, probably in two ways (1) by the outward movement of ciliated epithelium, (2) by the inhibitory or destructive action of the nasal secretion

THE LARYNX

Cultures have also been made directly from the larynx. Jundell,¹⁵ by means of a concealed swab on a sound, and with the aid of a laryngeal mirror, made direct cultures from forty-three cases, 90 per cent of which were sterile

TRACHEA AND BRONCHI

It is now generally agreed that the problem cannot be approached by using necropsy material, for it is found that the pneumococcus was found as often in normal lungs at necropsy as in the primary and secondary pneumonias

Thus Durck¹⁶ found the pneumococcus present in the lung in 92 per cent of thirteen necropsies on children free from any macroscopic or microscopic patches, while in forty-one cases of primary and secondary pneumonia he found the pneumococcus present in 84.6 per cent

¹⁵ Jundell, I. Ueber das Vorkommen von Mikroorganismen in den normalen Luftrohren, Skandin Arch f Physiol, 1897-9, vii, 284

¹⁶ Durck, H. Ueber die Aetologie und Histologie der Pneumonie im Kindesalter, u d Pneumonie im Allgemeinen, Deutsch Arch f klin Med, 1897, lvi, 368

Similarly, Norris and Pappenheimer¹⁷ found the pneumococcus in 86 per cent of twenty-eight cases affected with lobar pneumonia or other pulmonary lesions, while in fourteen cases of normal lungs, they found it in 93 per cent

The reasons for this have been well brought out by the latter authors. They placed one half dram of a broth culture of *Bacillus prodigiosus* in the mouths of patients after death, and found that in 50 per cent of cases this organism was present in the lung juice at necropsy

One must also consider the agonal invasion of organisms from the bowel. Thus Ritchie¹⁸ found the colon bacillus in 60 per cent of his necropsies, in all of which he regarded the bacilli as secondary invaders. The proportion of cases in which they were present, and the number of colon bacilli found were strictly proportional to the number of hours that elapsed before the necropsy was made

The same objection applies to slaughter-house material, since we cannot prevent the aspiration of fluid into the trachea and lungs during the death agony. Hence the problem has been approached by experiments with laboratory animals. In the laboratory experiments, the animals were killed by a knock, the trachea tied off immediately, the chest opened by cutting the diaphragm and lower ribs. Pieces of lung, mucous membrane, and mucus from the larynx, trachea, and bronchi were placed in bouillon and plated on agar. As a still further refinement the trachea ligature was placed before killing the animal, so that the fatal blow and the tying of the ligature would occur at the same time

Hildebrandt,¹⁹ Klipstein,²⁰ Gobell,²¹ Barthel,²² Becco,²³ and W. Muller²⁴ all came to the conclusion that the bronchi and lungs in normal animals are sterile

17 Norris, C, and Pappenheimer, A. A Study of Pneumococcus and Allied Organisms in Human Mouths and Lungs after Death, Jour Exper Med, 1905, vii, 450

18 Ritchie, W. T. The Bacteriology of Bronchitis, Jour Path and Bacteriol, 1901, vii, 1

19 Hildebrandt, G. Experimentelle Untersuchungen über das Eindringen pathogenen Mikroorganismen von den Luftwegen und der Lungen aus, Beitr z path Anat u Physiol, 1887, ii, 4111

20 Klipstein, E. Experimentelle Beiträge zur Frage der Beziehungen zwischen Bakterien und Erkrankungen der Athmungsorgane, Ztschr f klin Med, 1898, xxxiv, 191

21 Gobell. Ueber der Infection der Lungen von den Luftwegen aus, Dissertation, Marburg, 1897

22 Barthel, T. Ueber den Bakteriengehalt der Luftwege, Centralbl f Bakteriologie u Parasitenk, 1 Abt 1898, xxiv, 401, 433, 576

23 Becco, L. La flore bactérienne du poumon de l'homme et des animaux, Abstr, Centralbl f inn Med, 1900, xvi, 846

24 Muller, W. Experimentelle und klinische Studien über Pneumonie, Deutsch Arch f klin Med, 1901, lxxv, 513

In transferring these results to man, we have some direct evidence obtained by Kirchsteiner,²⁵ who made cultures on executed criminals

To the foregoing we may add the theoretical considerations of F Müller.²⁶

1 Hemorrhagic infarcts of the lungs do not lead to abscess formation

2 Surgically, lungs heal *per primum*

3 In serous exudates into the pleura and pericardium, one often punctures the lung and nothing follows. If, however, one punctures a lung which contains bacteria empyema may follow

4 If bacteria were usually present in the lung, the same as in the mouth or intestine it would be incomprehensible why mouth secretion or food which enters through insufficient closing of the glottis, is so dangerous and often leads to pneumonia (ex bulbar paralysis)

All the experimental work is in harmony and from it one must conclude that the normal lung is sterile and that the bacteria are either filtered out in the nose or are destroyed after reaching the lung

The nose with its deviated channel lined with ciliated epithelium, which rapidly moves the bacteria outward, is admirably adapted to protect the lung from dust and bacteria under ordinary conditions. If, however, the dust or bacteria content exceeds a certain stage, this protection is not sufficient, as is shown by the experiments of Hildebrandt¹⁹

Clinically we also have evidence that this protection is only relative, as is shown by the changes produced in the lung through the inhalation of dust in the various occupations of which anthracosis is the most prominent example. Here we find that dust has penetrated the respiratory tree and is deposited in the lung, lymph channels, and lymph nodes. That the bacteria are destroyed after entering the lung is shown by the fact that normal lungs are sterile; also by the experimental introduction of bacteria, both virulent and avirulent, into the lung

COLLECTION OF SPUTUM FOR SPUTUM CULTURES

We are all familiar with the cups sent to the clinical laboratory for the students to make stains for tubercle bacilli, and Gram stains. These cups contain the accumulation of the expectoration of from twelve to twenty-four hours, of post-nasal hawkings, mouth washes, and remnants of food. This mixture incubated at room temperature for about twelve hours is then labeled and sent to the laboratory for

²⁵ Kirchsteiner. Personal communication to F Müller.

²⁶ Müller, F. Der Keimgehalt der Luftwege bei gesunden Thieren. München med. Wehnschr. 1897. xlv, 1382

examination These samples are valueless, and time-consuming even for an ordinary smear for tubercle bacilli, or for a Gram stain, since the most promising piece picked out will probably be a tenacious portion very likely derived from the postnasal space It does not seem amiss to emphasize that for sputum cultures to give any results, the *sputum must be as carefully collected as blood or urine that is to be used for cultural purposes* The sputum should be collected in a sterile dish, the mouth should be clean, and the patient interested in his case, and told that an attempt is being made to find the cause of his cough The patient should be instructed to expectorate into the bottle or dish only what he is certain comes from his "boots," and also made to understand that very little is wanted, but that that little must be choice

It is useless to give the dishes to the night nurse on the ward, for we all know how busy she is with the ordinary routine work, and how an attempt will be made to collect the sputum at a moment's notice like a specimen of urine

The specimen when collected should be plated at once If that is not possible, it should be kept on ice

CHARACTER OF SPUTUM

It is impossible to predict the nature of the infection from the character of the sputum If, however, one wants to get a good idea as to the nature of the sputum, the presence of casts, etc., there is no better way than to suspend it in a solution of salt or bouillon, in a Petri dish and to wash it by means of a sterile platinum needle The general impression is that the sputum from pneumonia is very tenacious, yet it is the most difficult sputum to wash This is what one should expect, for the sputum from a pneumonic process is serosanguineous, while that from the bronchial tree is mucoid and tenacious It is important to bear this in mind when culturing pneumonic sputum

METHOD OF CULTURING THE SPUTUM

The sputum must be washed as thoroughly as its tenacity will permit, from five to ten successive sterile Petri dishes of bouillon or salt solution (To observe the effect of this washing one need but make a smear before and after washing the specimen) A portion was then macerated in a tube of bouillon and several loops transferred to fresh blood agar plates, then spread evenly over the surface by means of a bent glass rod which had been previously sterilized To assist in the even distribution of the washed sputum on the plates, a small amount of sterile bouillon was added These plates were incubated from twenty-four to seventy-two hours and examined every day All the colonies appearing in considerable numbers were subcultured and placed on all laboratory mediums, including blood agar, and the various sugars when these were necessary for differential diagnosis In case of mixed infections the relative number of colonies were noted by actual and approximate counts When an indefinite or negative result is obtained, it is important to make one or more subsequent

cultures Even with the best of care one may fail to get the right kind of specimen This is especially true in dealing with patients who are far below the average in intelligence Then, too, certain stages of the disease yield better sputum specimens than others

It is also important to use freshly prepared blood agar plates, as emphasized by Schottmuller²⁷ The sugar medium was enriched with hydrocele fluid according to method of Holman,²⁸ as recently reported in the *Journal of Infectious Diseases*²⁹ Atypical strains of pneumococci and streptococci were kept in stock for further study All the pneumococcus and streptococcus strains were tested for their fermentative action on the various sugars, also their hemolytic power on fresh blood agar, their solubility by means of bile, and their ability to coagulate milk

Many of the chronic cases were repeatedly cultured with a view of determining the constancy of the infection It has been the belief of some that the flora is an ever-changing one Some of these cases have been followed for four years and the type of the organisms and peculiarities in regard to hemolysis of blood, fermentation of sugars and coagulation of milk, have always been the same in a given case

RESULTS OBTAINED

If the foregoing conditions in regard to collection of sputum and method of culturing are observed, it will be found that in acute conditions remarkable plates will result and that, as a rule, one organism will be present practically in a pure culture This is especially true if the acute process occurs in a previously normal lung If the lung is the seat of an old chronic process, an acute involvement will also show the type of infection in a practically pure state, but the infection may be mixed, owing to the presence of organisms causing the chronic process

Table 1 gives a summary of the results of over 600 sputum cultures in 459 cases of infections of the respiratory tree The figures in the table represent the number of cases of the particular infection as indicated on the left of the table, and the organism causing this infection as indicated at the head of the table, for example bronchopneumonia, there were 42 cases and 56 cultures, 13 of the cases were caused by the pneumococcus, 1 case by the *Streptococcus mucosus capsulatus*, 1 by the pneumococcus and influenza mixed, 21 cases by the influenza alone, 1 by an atypical Friedlander, 1 by the *Micrococcus catarrhalis* In 4 cases no result was obtained

27 Schottmuller, H Die Artuntersuchung der fur den Menschen pathogenen Streptokokken durch Blutagar, Munchen med Wchnschr, 1903, 1, 849, 909

28 Holman, W Personal communication

29 Holman W A Method for Making Carbohydrate Serum Broth of Constant Composition for Use in the Study of Streptococci Jour Infect Dis 1914, xv, 209-227

TABLE 1.—SUMMARY OF RESULTS OF OVER 600 SPUTUM CULTURES IN 459 CASES OF INFECTIONS OF THE RESPIRATORY TREE

[illegible]

It will be seen from Table 1 that 95 per cent of the infections are represented as single type infections either pure or in such preponderance that no doubt could be left as to the etiological agent. This large percentage is due to the fact that 87 per cent of the cases were acute cases, and that in the 13 per cent of chronic cases, many were also acute infections on top of an old process.

The material was drawn chiefly from the wards of the Johns Hopkins Hospital, many from my own private practice and that of friends. The hospital cases have the advantage of carefully worked out records, Roentgen ray examinations, and in many of the fatal cases, necropsy findings.

PNEUMOCOCCUS

It will be seen in Table 2 that while the pneumococcus is practically the sole cause of acute lobar pneumonia, it is also the etiological agent in 62.4 per cent of all the respiratory infections below the larynx, and that together with the influenza bacillus it is the cause of 90.94 per cent of all nontuberculous infections below the larynx.

It will also be seen that the pneumococcus is present in 55.5 per cent of all cases of acute laryngitis and that with the influenza bacillus it is the cause of practically 75 per cent of all acute infections of the larynx. In the infection of the head, nose, sinuses, tonsils and ear, the pneumococcus and influenza bacillus diminish in frequency, being present in 31.29 per cent of cases, while the streptococcus assumes the predominant rôle, being present in 48.85 per cent of the cases.

STREPTOCOCCUS

It will be seen that the streptococcus was present in only seven cases out of 244 cases cultured, or in 3.1 per cent of all infections below the larynx, and that when present, it was associated with bronchiectasis, lung abscess, and acute bronchitis. This is somewhat at variance with the reports usually current in the textbooks. McPhedran³⁰ states that the streptococcus is found almost alone in infantile bronchitis of measles, gastro-enteritis and syphilis. It might be argued that this difference of findings was due to the fact that my material was limited almost entirely to infections in adults, and that in children the streptococcus plays a more important rôle. This, however, is not borne out by the findings of Holt,⁴ and of Wollstein.³ In sputum cultures of 257 cases of respiratory infections, Holt found the streptococcus "*rarely* as the predominant type, usually only in small numbers, in one half of the patients and in one third of the cultures taken."

30 McPhedran, A. Modern Medicine, 1907, III, 640

In 138 necropsies, the streptococcus was found alone only *once* and present only 43 times

To show how infrequently the hemolytic streptococcus type is found in the lungs, the following case is of interest

TABLE 2—SUMMARY OF THE NUMBER OF TIMES EACH ORGANISM WAS FOUND IN THE VARIOUS RESPIRATORY INFECTIONS ENUMERATED IN TABLE 1

BRONCHI AND LUNGS		Per cent
138	Pneumococcus	62.44
63	Influenza	28.5
7	Streptococcus	3.16
2	Friedlander	0.9
2	Micrococcus catarrhalis	0.9
1	Staphylococcus pyogenes aureus	0.45
6	Staphylococcus cereus albus	2.71
1	Diphtheria	0.45
1	Undiagnosed	0.45
<hr/>		<hr/>
221		100.00
LARYNX		
20	Pneumococcus	55.55
7	Influenza	19.41
5	Micrococcus catarrhalis	13.9
1	Staphylococcus pyogenes albus	2.8
3	Staphylococcus cereus albus	8.33
<hr/>		<hr/>
36		100.00
HEAD		
24	Pneumococcus	18.32
17	Influenza	12.97
64	Streptococcus	48.85
18	Staphylococcus pyogenes albus and aureus	13.74
3	Micrococcus catarrhalis	2.29
1	Undiagnosed	.76
2	Hoffman's bacillus	1.52
1	Typhoid and colon	.76
1	Bacillus pyocyaneus	.76
<hr/>		<hr/>
131		100.00

CASE 1—E. B., aged 32, was admitted to the surgical ward Feb. 17, 1913, with a swelling in the neck beneath the left jaw which was incised and drained the following day. The temperature rose to 105 on the 20th, from which time it gradually fell, reaching 100 on the 26th, when it again rose to 105. He complained of severe headache and at times was irrational. On March 1 he was transferred to the medical side. At that time the blood culture was negative. On the 5th he was in a stupor, but could be aroused. The heart and lungs were not involved. A lumbar puncture was done but the spinal fluid was found negative. On the 10th he developed a fluctuating swelling on the left wrist, which was evacuated on the 12th. This pus contained the *Streptococcus pyogenes*. On the 12th a blood culture showed the *Streptococcus pyogenes*. Two subsequent cultures also showed the *Streptococcus pyogenes*. On the 15th, another metastatic, suppurating, phlegmon developed subcutaneously on the left foot. March 21 a similar indurated fluctuating mass was opened over the lower sacrum and a cup of pus was evacuated. The temperature at that time was 105. On the 24th and 26th the blood cultures were negative. March 27 an impairment developed in the right lower back, and the patient developed an acute lobar

pneumonia from which he died on March 31. On the 28th a sputum culture was made and a pure culture of a typical, green, inulin-fermenting pneumococcus was isolated. Both cultures, the streptococcus from the blood and the pneumococcus from the pneumonia, were passed through all the sugars and subjected to all the differential tests so that no mistake was possible in identification. If one ever had a right to expect a streptococcus process in the lungs it was in this case with repeated positive blood cultures of the *Streptococcus pyogenes* associated with multiple metastatic subcutaneous abscesses due to the same organism. Yet the terminal pneumonia was a typical pneumococcus affair.

INFLUENZA BACILLUS

The influenza bacillus was found in 28.5 per cent of cases of non-tuberculous infection below the larynx, in 20 per cent of the infections of the larynx and 13 per cent of the infections of the head.

While it is undoubtedly true that since the pandemic of 1889 and 1890 many of the so-called influenza epidemics have been found to be due to the pneumococcus, as has been shown by Curschman³¹ and Pollak,³² yet it certainly is a mistake to say "that in the last ten years it has sunken to the position of a saprophyte, found in bronchiectasis and tuberculosis, and that it is only sporadically dangerous and then only as a mixed infection."³³

It will be much more true to say that the rôle of the influenza bacillus has steadily risen, and that, next to the pneumococcus, it is one of the most important infectious agents found in pulmonary lesions, that it is not only present in pandemics and epidemics, but also the cause of approximately 30 per cent of the pulmonary lesions in interepidemic periods. If anything definite can be said about sputum cultures at all, it may be stated emphatically that the results are as convincing in regard to the influenza bacillus as they are for the pneumococcus. The cultures are so pure, the bacilli in such tremendous numbers, often 50,000 colonies on one plate made from a loopful of sputum, that no doubt can be left as to its etiological relation. The clinical process in these cases can, as a rule, be predicted in that the cases usually are not fatal, the toxemia less, and the pulse relatively slow.

These findings are in agreement with those of Lord,² who, in his influenza studies, found the influenza bacillus in pure cultures in 30 per cent of the cases of lung infections in the interepidemic periods.

31 Curschmann, H. Pneumokokken Influenza, München med. Wchnschr., 1909, li, 377.

32 Pollak, R. Bakteriologische Befunde bei eitrigen Bronchitiden, Wien klin. Wchnschr., 1908, xxi, 973.

33 Leichtenstern, O. Influenza, 1912, Ed. 2, Quotation from Kongress-Zentralbl. f. d. ges. inn. Med. u. ihrer Grenzgeb.

MICROCOCCUS CATARRHALIS

R Pfeiffer³⁴ first described a biscuit-shaped coccus, easily decolorized by Gram's stain, growing on ordinary mediums, but dying out quickly. More recently, Gohn and H Pfeiffer³⁵ gave a detailed description of the cultural characteristics, virulence, differential diagnosis and frequency of occurrence. They studied 132 cases, and found the coccus pure only once, in a case of a child who died from profuse bronchitis.

Hastings and Niles⁶ found it as the most frequent organism in their sputum cultures during the years of 1903 to 1910 inclusive. It was found pure in

- 1 case of acute laryngitis
- 4 cases of grip
- 1 case of acute bronchitis
- 1 case of asthma

Their conclusion is that while "it is usually considered as a common, secondary invader, it may and probably does assume pathogenic properties."

Niles and Meara³⁶ found the *Micrococcus catarrhalis* in a case of bronchopneumonia complicated with arthritis and peritonsillar abscess.

It will be seen in Table 1 that the *Micrococcus catarrhalis* was found pure in

- 1 case of bronchopneumonia
- 1 case of acute bronchitis
- 5 cases of acute laryngitis
- 3 cases of acute rhinitis

The case of bronchopneumonia is especially worthy of consideration.

CASE 2.—K P, aged 21, a sailor, was admitted with the following history. Two days before entering the hospital he was awakened from his sleep with dizziness, headache, and pain in chest. The pain in the side was more severe on breathing. Soon after onset he developed a cough with bloody expectoration.

The examination showed impairment of the right lower lobe, and suppression of breath sounds, indicating beginning consolidation of the right lower lobe. The leukocytes were 15,000. On the following day the breath sounds over the right lower lobe were suppressed, the note had a rather high pitch, and fine crackling râles were heard. The leukocytes had fallen to 8,700. The temperature on admission was 106, with a sharp crisis twelve hours later, remaining normal thereafter. Sputum cultures were made on the day of admission and on the two subsequent days. Each time a pure culture of the *Micrococcus catarrhalis* was found.

34 Pfeiffer, R. Die Mikroorganismen, Ed 3, 1896, personal communication to Kolle and Wassermann.

35 Gohn, A, and Pfeiffer, H. Der Mikrooccus Catarrhalis (R Pfeiffer) als Krankheitserreger, Ztschr f klin Med, 1902, xlv, 262.

36 Niles, W L, and Meara, F S. Lobar Pneumonia of Micrococcus catarrhalis and Bacillus coli communis, Am Jour Med Sc, 1911, cxli, 803.

There can be no question that this was a case of *Micrococcus catarrhalis* infection. It might be argued that the pneumococcus might have been absent in the sputum. Thus Hastings and Niles⁵ found it absent in 65 per cent of their cases of pneumonia, and Hastings and Boehm in 37 per cent of their cases. My own findings with 168 sputum cultures in 83 cases of pneumonia show that in a true pneumococcus pneumonia the pneumococcus is never absent unless the patients are moribund and too sick to expectorate. In two such cases, no result was obtained by sputum culture.

STAPHYLOCOCCUS GROUP

It is interesting to note with what rarity staphylococci were found in infections of the lungs and bronchi. The *S. aureus* was found only once, and that in a case of asthma, the *S. albus* once, mixed with the *Staphylococcus cereus albus*, also in asthma. In infections of the larynx, the *S. aureus* was never found, the *albus* once, and the *cereus albus* three times. Even in infections of the head, in which one surely has a right to expect the staphylococcus if anywhere, it was found only 18 times in 151 cases, only once in acute coryza, only once in 29 cases of sinus infections in which the culture was made directly to blood agar at operation, and not once in 11 cases of mastoid infections.

The same observations were made by Lord, who did not find the staphylococcus once in pure culture in 183 cases of pulmonary infections.

Hastings and Niles⁵ found the *Staphylococcus aureus* in 15 per cent of their cases, and in pure culture in 10 per cent as follows:

3 times in acute laryngitis
7 times in chronic bronchitis
6 times in lobar pneumonia
3 times in bronchopneumonia

The *Staphylococcus albus* was found in 6 per cent of the cases, pure in 2 per cent, twice in grip, and twice in acute bronchitis. Their findings may be explained by the failure to use blood agar except where smears made from the sputum indicated Gram-negative organisms. Consequently, they found the influenza bacillus only once in seven years, 1903 to 1910, while Wollstein in 1906 found this bacillus in 17 out of 61 cases of bronchopneumonia, and Holt, in the years of 1908 to 1910 found it in 110 out of 257 cases, or 42 per cent. One of the reasons for their failure to find the influenza bacillus in smears is that all our counter stains are diffuse stains, and it is very difficult to distinguish delicate Gram-negative organisms from the debris on the slide. Hence the only safe guide is to use blood agar in all cases. It is also certain that nearly equally discordant results will be obtained

with the pneumococcus and streptococcus unless blood medium is used. The failure of Hastings and Niles to find the pneumococcus in the sputum of 43 out of 66 cases of lobar pneumonia, is a striking confirmation of the above view.

Holt found the *Staphylococcus aureus* as a mixed infection in 233 out of 257 cases of sputum cultures of children ill with pneumonia, bronchitis, tracheitis, and laryngitis. In 136 necropsies on children, it was also found alone 26 times, 8 times in pneumonia, 6 times in bronchitis, 8 times in pulmonary tuberculosis, and 4 times in non-respiratory cases. These necropsy findings hark back to the same discussion of the value of necropsy findings, and again illustrate the contention of Norris and Pappenheimer,¹⁹ who found the pneumococcus as often in normal lungs at necropsy as in lungs affected by a pneumonic process. Similar results were found by Durck in children.

The method of obtaining the sputum on swabs in children explains the mixture of the infection in their sputum cultures. From the beginning I avoided sputum obtained from children, little faith being placed in the source of the sputum obtained by introducing a swab into the child's throat and making it cough or gag. This idea is confirmed by Holt's findings,⁴ in which he states that pure cultures were practically never obtained, and his conclusions are not at all convincing when he says, "what a mixed infection the acute pneumonia of early life is, the table shows strikingly."

TYPHOID BACILLUS

All the earlier investigations on the presence of typhoid bacilli in the consolidations of the lungs complicating typhoid fever were made on necropsy material and hence are subject to the same objections that are brought against all necropsy material on account of the agonal and postmortem invasions of bacteria into the lung.

Since 1887 sputum cultures were made by M. W. Richardson,³⁷ Stuhlern,³⁸ Dieudonne,³⁹ Edel,⁴⁰ Glaser,⁴¹ Jehle,⁴² Rau⁴³ and others

37 Richardson, M. W. Upon the Presence of Typhoid Bacilli in Urine and Sputum, *Boston Med and Surg Jour*, 1903, cxlvi, 152.

38 Stuhlern, V. Beitrag zur Bakteriologie der Lobaren Typhus-Pneumonien, *Centralbl f Bakteriol*, etc., 1 Abt Orig, 1900, xxvii, 353.

39 Dieudonne, A. Zur Bakteriologie der Typhus-Pneumonien, *Centralbl f Bakteriol*, etc., 1 Abt, 1901, xxx, 481.

40 Edel, P. Typhus Bacillen im Sputum, *Fortschr d Med*, 1901, xix, 301.

41 Glaser, F. Die Bedeutung der Typhusbacillen bei Erkrankungen des Respirationsapparatus in Gefolge des Ileotyphus, und sein Auftreten im Auswurf, *Deutsch med Wchnschr*, 1902, xxviii, 772, 793.

42 Jehle, L. Ueber den Nachweis von Typhusbacillen im Sputum Typhuskranker, *Wien klin Wchnschr*, 1902, xv, 232.

43 Rau, R. Ueber das Auftreten Typhusbacillen im Sputum, und uber ein typischen Fall von Pneumotyphus, *Ztschr f Heilk*, 1904, xxv, 385.

Edel examined eleven cases of bronchitis and found no typhoid bacilli

Jehle examined twenty-two cases of uncomplicated bronchitis and found the typhoid bacillus present only four times and only once in pure culture

Glaser reported two cases of pneumonia complicating typhoid fever in which the pneumococcus was present each time. The typhoid bacillus was also present, but to show how *nebensächlich* the typhoid bacillus is, he cites the following case

Man, aged 45, was admitted with typhoid fever and developed pneumonia eight days later, dying on the fifteenth day of his pneumonia. The sputum showed only pneumococci and no rods, on the fourteenth day of his pneumonia a lung puncture was made and typhoid bacilli were obtained in pure cultures. The patient died the next day, and the cultures made at necropsy showed numerous pneumococci with only occasional typhoid bacilli

Edel reports one case of pneumonia accompanying typhoid fever in which he found the typhoid bacillus. He, however, does not exclude the pneumococcus or the influenza bacillus

Stuhlern reports two cases in which he found the pneumococcus and staphylococcus besides the typhoid bacillus

Dieudonne reports one case in which he found chiefly pneumococci with only a few rods

Jehle reports a case of lobular pneumonia complicating typhoid which he examined six times and found the typhoid bacillus five times in pure cultures. The necropsy also showed a great many typhoid bacilli

My own observations are limited to three cases in none of which was the typhoid bacillus present. For instance

CASE 3—H B was admitted to the hospital January 12 with typhoid fever. The blood culture was positive for typhoid. Three days after admission he developed an impairment over the right lower lobe, with suppression of the breath sounds and numerous cracking râles. This condition persisted for one month and then cleared up. Ten days after admission the sputum showed a pure culture of the influenza bacillus

Except for the case of Jehle, there are no cases on record, as far as I know, in which the typhoid bacillus seems to have been the only organism present. He is the only one who attempted to use blood medium (rubbed the surface of his plate with sputum and sterile horse blood). As was shown above, the influenza bacillus is the cause of 30 per cent of all lung infections. It will thus be seen that in this percentage of cases, the typhoid bacillus might have been found alone, and yet not have been the etiological agent

That one would expect the typhoid bacillus in the bloody serum of pneumonia complicating typhoid fever needs no elaboration, since one knows that in typhoid fever a bacteremia exists

One must then come to the conclusion of A. Frankel,⁴⁴ who as early as 1899 stated that while not denying the possibility that the typhoid bacillus may cause a pneumonic process, he felt that the typhoid bacillus had only a secondary significance.

It must however be expected, that in cases of lung infarct followed by lung abscess the typhoid bacillus may be the only organism present. Flexner and Harris,⁴⁵ Robinson,⁴⁶ and Glaser⁴⁷ each report such a case.

In recent years considerable work has been done on the presence of typhoid bacilli on the tonsils and in the pharynx of patients ill with typhoid fever with special reference to the epidemiological aspect.

Manicatide⁴⁸ found it in 70 per cent of cases, and Purjesz and Perl⁴⁹ in 20 per cent of the cases.

Gaetgens⁵⁰ found it only twice in thirty-two cases, in both of which there were typical throat ulcers.

Schutz⁵¹ examined twenty-three cases and made cultures by using bile, Drigalski, and Endo mediums and found all negative. His conclusions are that typhoid bacilli are found only if ulcerations are present.

COLON BACILLUS

The colon bacillus was never found during life in this series of over 600 sputum cultures. There are, however, scattered reports in the literature.

In 1895, Hitzig⁵² reported a case of lung gangrene from the sputum of which he isolated an atypical colon bacillus.

In 1908 Schrotter and Weinberger⁵³ reported a case of lobular pneumonia in which the colon bacillus was obtained, often in pure

44 Frankel, A. Zur Lehre von den Affectionen des Respirationsapparatus beim Ileo-Typhus, *Deutsch med Wchnschr*, 1899, xxv, 231, 252.

45 Flexner, S., and Harris, N. Typhoid Infection without Intestinal Lesions, *Bull Johns Hopkins Hosp*, 1896-97, vii, viii, 259.

46 Robinson, G. C. Rôle of Typhoid Bacillus in the Pulmonary Complications of Typhoid Fever, *Jour Infect Dis*, 1905, ii, 498.

47 Glaser, F. Die Bedeutung der Typhusbacillen bei Erkrankungen des Respirationsapparatus in Gefolge des Ileotyphus, und sein Auftreten im Auswurf, *Deutsch med Wchnschr*, 1902, xxviii, 772, 793.

48 Manicatide, M. Sur la recherche du bacille typhique dans le pharynx des malades de la fièvre typhoïde, *Centralbl f Bakteriöl*, 1908, xlv, 221.

49 Purjesz, B., and Perl, O. Ueber das Vorkommen der Typhusbazillen in der Mundhöhle bei Typhuskranken, *Wien klin Wchnschr*, 1912, xxv, 1494.

50 Gaetgens, W. Ueber die bakteriologische Typhusdiagnose auf Grund von neueren, in der praktischen Typhusbekämpfung gesammelten Erfahrung, *Berl klin Wchnschr*, 1912, xlix, 296.

51 Schutz, F. Ueber das Vorkommen von Typhusbazillen auf den Tonsillen Typhuskranker, *Deutsch med Wchnschr*, 1913, xxxix, 451.

52 Hitzig, T. Beiträge zur Aetiologie der putriden Bronchitis, *Arch f path Anat u Physiol u f klin Med*, 1895, cxli, 28.

53 Schrotter, H., and Weinberger, M. Zur Kenntnis der Kolibazillose der Respirationsorgane, *Wien klin Wchnschr*, 1908, xxi, 505.

cultures Nests of influenza-like bacilli and streptococci were also present during the first week, and it is not at all clear that the colon bacillus was the etiological agent

In 1911, Niles and Meara³⁶ report an atypical case of bronchopneumonia, also complicated with diphtheria and erysipelas, in which they found the colon bacillus No mention is made of the medium used, and unless blood agar was used the findings are in grave doubt

One must conclude that the evidence for the colon bacillus is even less convincing than that for the typhoid bacillus

DIPHTHERIA BACILLUS

The diphtheria bacillus was found once in a case of chronic bronchitis associated with an unidentified Gram-negative, motile bacillus These organisms were found repeatedly over a period of one year in an abundant, green, mucoid sputum The diphtheria bacillus was avirulent for guinea-pigs

FRIEDLANDER BACILLUS

We hear much about the Friedlander bacillus, possibly because of the early discussion as to its relation to the etiology of pneumonia

It therefore must seem rather surprising to find that it occurred only twice in 600 sputum cultures, nor was it present in all the subcultures made from isolated colonies accompanying the dominant organism

Of the two cases in which it did occur, one was a case of chronic bronchitis in a woman of 60, the other a case of bronchitis, bronchopneumonia, and bronchiectasis The dilated bronchi ended everywhere with cavities varying in size from grapeseed to hazelnut In this latter case a pure culture of an atypical Friedlander was obtained, a Gram-negative, non-motile, capsulated bacillus, not fermenting any of the sugars, not changing milk to acid or producing coagulation

UNITY OF INFECTION OF THE RESPIRATORY TREE

It will be seen from this study that the same organisms produce the infections of the upper and lower respiratory tract If one reviews the reports thus far made on acute coryza, one would be led to believe that an entirely different flora is the cause of the nose infections from that of the chest infections Yet it is contrary to what one should expect, and what the results from this series of cases indicate

The character of the sinus infections supports the results obtained from acute coryza infections, for it would seem inconceivable that the infections of the sinuses should be the result of a different organism from that of the infections of the nose, from which they so frequently result and with which they have a direct anatomical connection

VALUE OF SPUTUM CULTURES

It seems almost needless to say that all our knowledge of prophylaxis and specific therapy starts with our knowledge of the etiology of a given disease. Much of the diagnosis, the course of the disease and its complications are also dependent on a knowledge of its etiology. While the specific therapy may not immediately be at hand, we are at least laying the foundation-stones for such a therapy in the future.

It is also necessary that we should know the various pathological processes a given organism will produce. As a result of such studies we have learned that the influenza bacillus may produce lesions and clinical symptoms indistinguishable from those of the tubercle bacillus as shown by Lord.² In a subsequent paper we shall find that the pneumococcus also may produce chronic lesions extending over many years. It used to be the conclusion that all chronic chest conditions must be tuberculous whether the tubercle bacillus was found or not, and that is still the attitude to a large extent. By means of sputum cultures we may place against this negative evidence, the positive evidence of a definite organism in the sputum, which organism may explain the cause of the chronic condition. By following these cases over long periods with subsequent necropsy records, we are able to make an important contribution to our knowledge of pulmonary conditions.

If we now come to the practical, everyday interest of sputum cultures to physicians in practice, we have here, in a great many cases, a means of an early, positive diagnosis. In private practice the family wants to know, and often becomes very restless and may disturb one's peace and happiness unless such a diagnosis is made.

As examples

CASE 4—A young man, aged 20, in a well-to-do family contracts an acute infection with severe cough, with a temperature rising to 103, somewhat of the remittent type. The lung findings point to a consolidation of a lower lobe. Pneumonia is the diagnosis. Fourteen days have elapsed and the crisis has not occurred, the cough is still very persistent, the temperature still reaches 103 in the evening, more remittent in type, tuberculosis is feared. A consultant is called, the diagnosis is still vague, we are still guessing. Tubercle bacilli, though looked for, have not been found. As a last resort, a sputum culture is requested. A pure plate of influenza bacilli with about 50,000 colonies results, one that you like to show around. Everybody is happy, a diagnosis has been made, and also a very reasonable prognosis.

CASE 5—C S, aged 34, was admitted to the hospital March 18, eight days after onset of his illness, complaining of cough and tightness in chest. Five days before admission he stopped work and was feverish. Patient did not look especially ill, and on physical examination showed impairment of the left base with distant breath sounds and slight bronchovesicular breathing. One could not definitely say that patient had pneumonia. The leukocytes were 18,000. The physical signs were never definite, and on March 25 a diagnosis was made.

of probable pleurisy with effusion on the left side. On March 29, on exploratory puncture, 10 cc of straw-colored fluid were obtained, not blood stained. The cell count was 3,300, 69 per cent of which were of the small mononuclear type. The culture from this fluid was negative. This clear fluid, with extremely low cell count and negative culture, together with the atypical physical signs and the absence of toxic symptoms, put the diagnosis of pneumonia still further in doubt and strongly suggested tuberculosis. The blood culture was negative. Twelve sputum examinations were made for tubercle bacilli with negative results. A sputum culture was made on the 21st and a *bronchial cast was found* which when plated gave a beautiful plate of pure pneumococcus colonies. Further cultures were made on March 22 and 24 with the same results. The subsequent course was uneventful.

Here an absolute diagnosis of a pneumococcus infection was made on March 21 while eight days later, the clinical diagnosis of the nature of the process was still in doubt, and might have remained in doubt, with an unhappy diagnosis and prognosis to the patient. It is a simple enough matter in a large hospital, and especially in a public ward, to await developments and to make a diagnosis after the patient is well and discharged, but one can easily foresee the possibilities of such a case in private practice, in a nervous family, and with people of means.

It is also important that we should think in definite causes and effects. Blood cultures in lobar pneumonia are positive in about 30 per cent of cases. In other pulmonary conditions they are practically always negative, and while we can record the symptoms and physical sign, our ultimate etiological diagnosis is usually guess work. In four consecutive necropsies, Park⁵⁴ found the influenza bacillus in pure culture in a case believed from the symptoms to have been due to the pneumococcus, and in two of the three cases believed to have been due to it, it was entirely absent. Except for these examinations, the clinician would have been of the opinion that he had clearly diagnosed the cases, while in fact, he was wrong in three out of four.

The following example illustrates how difficult it is to arrive at a true conclusion in regard to etiology unless sputum cultures are made.

CASE 6—W. A., aged 34, was admitted to the hospital Dec 4, 1912. His illness began four years previously, following an exposure. The patient began to take cold easily, especially in the winter. The present attack began four weeks previously, with cough, expectoration, and smothering sensation in the chest. He expectorated large amounts of yellowish sputum, not blood-stained. He had no night sweats. On physical examination he showed a slight cyanosis and dyspnea, with palpable and audible rhonchi, but with no impairment of the percussion note. On auscultation there were numerous, coarse, bubbling, moist râles, which exploded in showers at the height of inspiration. The impression was that of an acute bronchitis, perhaps influenza. December 6 it was noted that the percussion note had a tendency to box-like resonance, and crackling râles were heard throughout both lungs. The summary of this examination indicated signs of acute bronchitis, probably associated with bronchopneumonia.

⁵⁴ Park, W., and Williams, A. Pathogenic Micro-Organisms, 1910. Ed. 4, p. 357.

An old emphysema was assigned as the cause of the cyanosis. Tuberculosis was ruled out, and either an influenza or a pneumococcus infection was suggested. The features during the remaining stay were dyspnea, cyanosis, cough and abundant expectoration. Generalized miliary tuberculosis was also suggested. December 10 the patient became an ashen hue and was covered with profuse perspiration. The lips were intensely blue, pulse was rapid and palpated with difficulty at the wrist. He was given oxygen inhalations. December 11, a high degree of emphysema was suggested, with bronchitis and bronchopneumonic patches. On the 13th the question of miliary tuberculosis was again considered. A probable influenza or pneumococcus infection was also suggested. The leukocytes varied between 8,000 and 10,000. The Calmette reaction was negative. Tubercle bacilli were not found. The Roentgen ray diagnosis was a dilated heart and aorta. The patient was discharged on the 23d, considerably improved. January 8 he was readmitted with the same physical signs as on previous admission, with the addition of purpura of the lower limbs. The diagnosis then was either chronic bronchitis and pneumonia, or a diffuse tuberculosis process in the lungs and the peritoneum. The patient died Jan 10, 1913, probably from acute cardiac dilatation.

The anatomical examination showed the lungs salmon red in color, with the bronchi definitely enlarged, everywhere ending in cavities, varying in size from grapeseed to hazelnut. These cavities were lined with a smooth thin membrane and filled with a mucoid purulent secretion. In addition there were scattered red, raised, consolidated patches in all of the lobes. The bronchi everywhere were dilated, intensely injected, containing a mucoid purulent secretion. The heart was dilated with hypertrophy of the right ventricle and auricle.

A sputum culture was made on December 7 and repeated several times. The sputum was grass green, mucopurulent. Gram-negative bacilli were seen in smears. The plates showed a pure culture of a Gram-negative, non-motile, capsulated bacillus, belonging to the Friedlander group. This organism was atypical in that none of the sugars were fermented nor did it produce acid or coagulation in milk.

Here is a case, going through two hospital admissions, and a complete necropsy, without an etiological diagnosis. All the most probable infectious agents were suggested. The influenza bacillus, the pneumococcus, and the tubercle bacillus, and in view of the etiological agents suggested, a pathological process was pictured, from bronchitis and bronchopneumonia, to miliary tuberculosis.

If, however, we do know the etiological agent, and if we have a reasonably exact knowledge of what various processes a given organism may produce, we are in a fair position to visualize the pathological process.

The sputum cultures have also played an important part in our interpretation of Roentgen-ray plates of the chest. In 1911 Dunham, Boardman, and Wolman⁵⁵ made an extensive study of the markings in the lung. As a result of this study nearly all the chronic infections were diagnosed as tuberculous, regardless of whether the tubercle bacillus was found or not, or whether the tuberculin reactions were

⁵⁵ Dunham, Boardman and Wolman. The Stereoscopic X-Ray Examination of the Chest with Especial Reference to the Diagnosis of Pulmonary Tuberculosis, *Bull Johns Hopkins Hosp*, 1911, *xii*, 229.

positive or not. The sputum cultures, however, gave us evidence of chronic influenza infections, and chronic pneumococcus infections, and it was shown that the chronic processes in the chest, due to these organisms, were indistinguishable by means of the Roentgen ray from those produced by the tubercle bacillus. The case cited in the introduction well illustrates this fact.

SUMMARY

1 Sputum cultures have been neglected because of the confusing results obtained, and the mixture of organisms found.

2 These results were due to unsuitable mediums and bacteriological methods.

3 By means of fresh blood agar plates, practically pure cultures can be obtained in 95 per cent of the acute nontuberculous infections of the respiratory tract of adults.

4 The pneumococcus is the cause of 62.44 per cent of all the nontuberculous infections below the larynx, and the influenza bacillus in 28.5 per cent. These two organisms cause 90.94 per cent of the infections of the bronchi and lungs, 74.96 per cent of the infections of the larynx, and 31.29 per cent of the infections of the nose, throat and sinuses.

5 The streptococcus, contrary to common belief and textbook reports, is only rarely the cause of infections in the lungs, and when found, is usually associated with complications such as lung abscess, bronchiectasis, carcinoma, etc. In infections of the head, however, it assumes the predominant rôle, especially in the tonsils.

6 The *Staphylococcus aureus* was never found to be the cause of the acute infections of the lungs or larynx and only once was it found in acute coryza and acute sinusitis.

7 The *Micrococcus catarrhalis* may cause rhinitis, laryngitis, acute bronchitis and acute bronchopneumonia. It was found in pure culture in three out of thirty-seven cases of acute rhinitis, five out of thirty-eight cases of acute laryngitis, and in one each of acute bronchitis and primary bronchopneumonia.

8 The colon and typhoid bacillus rarely if ever produce acute lesions in the lung. The typhoid bacillus, however, may produce lung abscess following an infarct.

9 There is a unity of infection of the respiratory tree. The same organisms which cause the infections of the bronchi and lungs, also cause the infections of the nose, sinuses and larynx.

10 Sputum cultures afford us an easy, quick, and reliable method of diagnosis of pulmonary infections. Since blood cultures are negative in 70 per cent of the cases of pneumonia and negative in nearly all of the other infections of the respiratory tree, it is practically the

only means of making an etiological diagnosis in the nonfatal infections

11 This etiological diagnosis is necessary for a rational advance in prophylaxis and specific therapy. It is also a great aid in making an early diagnosis, and helps us to give an intelligent prognosis. This is especially desirable in private practice.

12 By means of these cultures we have also obtained a wider knowledge of what lesions a given organism may produce. These cultures show that each organism may produce a variety of acute lesions. Especially valuable information is afforded in that they show that the influenza bacillus and pneumococcus may produce chronic lesions extending over many years. This has an especial bearing on differential diagnosis, in regard to whether or not a given chronic chest condition is tuberculous.

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THE RELATION OF THE ADRENALS TO THE PANCREAS *

F C MANN, M D, AND DELLA DRIPS, A B

MAYO CLINIC, ROCHESTER, MINN

It was noted at autopsy in a study of animals dying after the removal of both adrenals that the pancreas always presents a characteristic appearance. In color the gland is deep pink and contrasts quite strikingly with the faint white color of the normal pancreas. Because of their marked injection, it is possible to see all the vessels by transmitted light, even those leading to the small lobules stand out prominently. Histologically the islands appear prominent and the capillaries are engorged with blood. This appearance is only slightly simulated by that of the fatigued gland at the end of a long period of digestion. Since these changes in the pancreas were so marked and constant, we deemed them worthy of a separate investigation. This seemed especially desirable as accurate data in regard to the polyglandular theory are very scant. We found only one reference describing a seemingly similar condition of the pancreas. Sweet and Allen¹ noted that at necropsy of dogs from which the hypophysis had been removed the pancreas presented a striking red coloration like that seen at the height of digestion. Microscopic study, however, did not reveal any very marked changes.

Numerous experiments have been reported the results of which tend to establish the existence of a specific functional relationship between the adrenals and the pancreas. Hypotheses concerning this relationship are based on two facts: (1) That epinephrin produces glycosuria, and (2) that it decreases the flow of pancreatic juice. Investigation has failed to demonstrate that the glycosuric action of epinephrin is due to its primary effect on the pancreas. Lusk and Riche² conclude that the glycosuric action of epinephrin is due to vasoconstriction and not to inhibition of pancreatic function. Crowe and Wislocki,³ who recently investigated the subject, conclude that carbohydrate tolerance is not modified in an adrenalectomized animal. The

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1 Sweet J E, and Allen, A R. The Effect of the Removal of the Hypophysis in the Dog, *Ann Surg*, 1913, lvi, 485, 3 pl

2 Lusk, Graham, and Riche, J A. Animal Calorimetry. Paper VIII. The Alleged Influence of the Adrenals on Diabetic Metabolism, *THE ARCHIVES INT MED*, 1914, xiii, 673

3 Crowe, S J, and Wislocki, G B. Experimental Observation on Adrenals with Reference to Functions of their Interrenal Portions, *Bull Johns Hopkins Hosp*, 1914, xxi, No 284

most comprehensive work on the relationship of the adrenals to pancreatic secretion has been done by Pemberton and Sweet⁴ They demonstrate that the injection of epinephrin decreases or inhibits the flow of pancreatic juice and that the removal of the adrenals increases the pancreatic secretion From these observations they conclude that the adrenals have an inhibitory function over the pancreas Edmunds,⁵ in a study of the effects of epinephrin on the flow of pancreatic juice, concludes that the inhibitory action is due to the production of marked vasoconstriction

Two general methods were used to study the effect of adrenal insufficiency on the pancreas

A—We performed a series of experiments in which the flow of pancreatic juice was carefully observed after various procedures on the adrenals The experiments under this method may be considered in two general groups, the first comprising those experiments in which the flow was recorded in anesthetized animals, and the second those in which the flow was observed in unanesthetized animals

B—By means of special stains, we studied the histologic changes in the pancreas after these procedures

METHOD A FLOW OF PANCREATIC JUICE AND GROSS ANATOMIC CHANGES AFTER ADRENALECTOMY

Group 1—The general procedure in Group 1 was as follows All the animals were fasted for thirty-six hours prior to the time of experiment They were carefully anesthetized with ether Carotid blood pressure was usually recorded by a Huertle manometer, however, the blood pressure could be measured directly by means of a two way stop cock connected with a mercury manometer All readings for blood pressure were taken from the mercury manometer The flow of pancreatic juice was obtained by placing in the major pancreatic duct a cannula connected with a glass tube graduated in 0.01 cm Readings expressed in cubic centimeters, were taken for fifteen-minute intervals Blood pressure and flow of pancreatic juice were recorded hourly on an extension kymograph for a period of fifteen minutes Normal temperature conditions were approximated as closely as pos-

4 Pemberton, Ralph, and Sweet, J E The Inhibition of Pancreatic Activity by Extracts of Suprarenal and Pituitary Bodies, *THE ARCHIVES INT MED*, 1908, 1, 628-647, Further Studies on the Influence of the Ductless Glands on the Pancreas, *Ibid*, 1910, v, 466, Sweet, J E, and Pemberton, Ralph The Induction of Pancreatic Activity by the Removal of the Adrenals, *Ibid*, 1910, vi, 536, Pemberton, Ralph, and Sweet, J E Experimental Notes on the Influence of the Adrenals Over the Pancreas, *Ibid*, 1912, ix, 169

5 Edmunds, C W Further Study of the Relation of the Adrenals to Pancreatic Activity, *Jour Pharm and Exper Therap*, 1910-11, 11, 559, The Antagonism of the Adrenal Glands Against the Pancreas, *Ibid*, 1909-10, 1, 135

sible by the judicious use of an electric pad. Since the passage of acid fluid from the stomach might prove to be a disturbing factor, the pylorus was usually ligated. In some experiments the minor duct was ligated to see if the free communication of the major and minor pancreatic ducts which is present in the dog was complicating results.

Series A—In this series of five experiments, the flow of pancreatic juice was measured in normal anesthetized animals, the experiments usually extending over eight to sixteen hours. In general, our results corroborated those of Pemberton and Sweet. In one animal there was no flow, in the others there was a slight initial flow which increased as the blood pressure decreased. The following is a representative protocol.

Experiment 4 (Series A)—Oct 5, 1914. Large male bulldog in good condition. Weight 36 pounds. Had fasted thirty-six hours. Etherized at 7 30 a. m. Apparatus arranged to record carotid blood pressure.

Time	Pulse	Resp	Temp	B P	Pan Flow
7 45 a. m.	180	42	100.9	110	
8 15 a. m.	180	42	98.2	110	
8 15-8 30					04
8 30 a. m.	180	42	98.2	110	
8 30-8 45					01
8 45-9 00					015
9 00 a. m.	156	48	97.6	105	
9 00-9 15					005
9 15-9 30					000
9 30 a. m.	144	48	98.6	100	
9 30-9 45					000
9 45-10 00					000
10 00 a. m.	150	42	97.3	90	
10 00-10 15					
10 15-10 30					000
10 30 a. m.	130	46	97.4	85	
10 30-10 45					000
10 45-11 00					000
11 00 a. m.	158	48	98.2	85	
11 00-11 15					000
11 15-11 30					000
11 30 a. m.	132	36	98.8	90	
11 30-11 45					05
11 45-12 00					04
12 00 m.	180	42	101.2	90	
12 00-12 15					08
12 15-12 30					08
12 30 p. m.	180	42	101.4	90	
12 30-12 45					000
12 45-1 00					000
1 00 p. m.	180	42	101.2	90	
1 00-1 15					000
1 15-1 30					000
1 30 p. m.	180	48	100.6	105	
1 30-1 45					000
1 45-2 00					005
2 00 p. m.	156	48	100.6	105	
2 00-2 15					000
2 15-2 30					000
2 30 p. m.	156	48	101.6	100	
2 30-2 45					000

Time	Pulse	Resp	Temp	B P	Pan Flow
2 45-3 00					000
3 00 p m	180	60	101 8	100	
3 00-3 15					000
3 15-3 30					000
3 30 p m	180	60	101 8	100	
3 30-3 45					02
3 45-4 00					07
4 00 p m	180	60	101 1	80	
4 00-4 15					06
4 15-4 30					08
4 30 p m	180	48	101 2	80	
4 30-4 45					06
4 45-5 00					02
5 00 p m	180	48	101 9	76	
5 00-5 15					05
5 15-5 30					03
5 30 p m	180	36	102 2	75	
5 30-5 45					00
6 00 p m	180	36	102 4	60	
6 00-6 15					06
6 15-6 30					05
6 30 p m	180	42	101 6	60	
6 30-6 45					11
6 45-7 00					23
7 00 p m	180	42	101 0	50	
7 00-7 15					08
7 15-7 30					14
7 30 p m	150	42	100 4	50	
7 30-7 45					11
7 45-8 00					05
8 00 p m	180	36	100 1	45	
8 00-8 15					29
8 15-8 30					07
8 30 p m	150	30	100 1	40	
8 30-8 45					10
8 45-9 00					15
9 00 p m	180	36	100 6	38	
9 00-9 15					12
9 20 p m	Animal died				

Necropsy—Performed immediately after death. Pyloric ligature had held, allowing no leakage. Thick fluid in stomach, which was markedly acid. No food material found above colon. There had been no hemorrhage. All organs appeared normal grossly. The weight of the pancreas was 45 gm.

Series B—In this series of three experiments, after taking a control flow of pancreatic juice, the adrenals were quickly removed and the flow recorded until death. Our results again corroborate those of Pemberton and Sweet, although the increase we obtained is not so pronounced as they record. The following experiment is typical.

Experiment 2 (Series B)—Oct 18, 1914. Large white bull in good condition. Etherized at 8 20 a m. Considerable difficulty experienced in getting the cannula in the duct. Stomach not ligated. Normal pulse 210, respiration 42, temperature 99.2, and blood pressure 100 at 8 30 a m.

Time	Pulse	Resp	Temp	B P	Pan Flow
9 15 a m	168	42	99.2	85	
9 30 a m	162	42	98.8	95	
9 15-9 30					02
9 45 a m	Right adrenal was taken out				

Time	Pulse	Resp	Temp	B P	Pan Flow
9 30-9 45					04
9 51	Left adrenal was taken out				
9 45-10 00					05
10 00 a m	162	42	98.4	95	
10 30 a m	160	36	99.2	90	
10 45-11 00					01
11 00 a m	142	32	99.4	100	
11 00-11 15					04
11 15-11 30					03
11 30 a m	156	39	99.8	105	
11 30-11 45					03
11 45-12 00					05
12 00 m	180	36	99.6	105	
12 00-12 15					09
12 15-12 30					11
12 30 p m	180	60	99.2	105	
12 30-12 45					12
12 45-1 00					10
1 00 p m	180	60	99.2	65	
1 00-1 15	180	36	99.2	60	12
1 30-1 45					18
1 45-2 00					18
2 00 p m	180	40	99.8	50	
2 00-2 15					26
2 15-2 30					22
2 30 p m	180	42	99.9	45	
2 30-2 45					23
2 45-3 00					33
3 00 p m	160	36	99.8	40	
3 00-3 15					30
3 15-3 30					25
3 30 p m	132	34	100.2	32	
3 30-3 45					30
3 45-4 00					35
4 00 p m	162	42	100.4	35	
4 05 p m	Injected small amount of adrenalin which increased the blood pressure, but decreased the pancreatic flow				
4 16 p m	Injected nicotin which decreased blood pressure and pulse Pancreatic flow decreased at first, but it soon quickened				
4 22 p m	Animal died				

Necropsy—Performed immediately after death. No hemorrhage at the sites of operation. Pancreas grossly normal. The stomach contained about 150 cc yellow colored fluid, acid in reaction.

Series C—In this series of twelve experiments one adrenal, usually the right, had been removed some days previously. The remaining gland was removed through a lumbar incision at the time of observation. Blood pressure was decreased but slightly by the adrenalectomy. In every experiment of this series the flow of pancreatic juice was increased after the removal of the remaining gland, but this observation is inconclusive, inasmuch as in many cases the increase was no greater than occurred in the control toward the end of the experiment. A typical experiment follows.

Experiment 7 (Series C)—Oct 7, 1914 Large white bull bitch of gentle disposition whose weight was 11,942 gm The right adrenal had been removed two weeks previously The animal was in excellent condition Fasted thirty-six hours prior to the experiment Etherized at 8 a m and apparatus arranged to record blood pressure and pancreatic flow

Table as follows

Time	Pulse	Resp	Temp	B P	Pan Flow
8 30 a m	180	60	98.2	120	
8 45 a m	168	60	98.2	100	
9 00 a m	168	66	98.2	95	
9 00-9 15					04
9 15 a m					03
9 15-9 30	The remaining adrenal removed				
9 30 a m	174	60	98.0	95	
9 30-9 45					03
9 45-10 00					03
10 00 a m	150	54	95.2	105	
10 00-10 15					02
10 15-10 30					01
10 30-10 45					04
10 45-11 00					04
11 00 a m	150	54	95.2	115	
11 00-11 15					04
11 15-11 30					04
11 30-11 45					035
11 45-12 00					055
12 00 m	144	48	94.6	115	
12 00-12 15					03
12 15-12 30					07
12 30-12 45					085
12 45-1 00					075
1 00 p m	150	48	96.0	110	
1 00-1 15					08
1 15-1 30					07
1 30-1 45					085
1 45-2 00					075
2 00 p m	150	48	96.1	80	
2 00-2 15					09
2 15-2 30					09
2 30-2 45					06
2 45-3 00					06
3 00 p m	120	24	96.1	55	
3 00-3 15					05
3 15-3 30					06
3 30-3 45					06
3 45-4 00					08
4 00 p m	204	42	97.0	35	
4 00-4 15					08
4 15-4 30					12
4 35 p m	Animal died				
Cannula inserted					

Necropsy—Performed at once Site of operation in excellent condition No hemorrhage No leakage through the pyloric ligature Acid found in the stomach All the other organs normal grossly Weight of the pancreas 35 gm

Series D—In this series of five experiments, both adrenals were removed under sterile conditions, at the same time or at different operations The pancreatic flow was studied after development of various degrees of adrenal insufficiency We found that in an animal which had developed none of the symptoms of adrenal insufficiency

the pancreas, while active, showed no increase over the controls. In every animal studied after the development of the signs of insufficiency, the pancreas was found to be secreting but usually a scarcely appreciable amount. The following experiment is a record of the greatest flow obtained in this series.

Experiment 5 (Series D)—Adult male mongrel. On February 17, 1915, the left adrenal gland was removed. The animal quickly recovered from the operation.

Date	Time	Pulse	Resp	Temp
3/1/15	5 30 p m	73	20	101.9
3/2/15	8 00 a m	78	20	102.3
	10 00 a m	Remaining adrenal gland removed		
	3 30 p m	135	20	102.8
	5 30 p m	142	21	103.2
3/3/15	2 30 p m	142	20	103.2
3/4/15	8 00 a m	150	22	103.1
	9 30 a m	136	22	102.4

Up to this time the animal appeared normal in every respect. Ate and drank regularly and showed no signs of muscular weakness.

3/4/15	2 55 p m	120	20	102.1	Normal data
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ANIMAL ETHERIZED

3 00 p m	175	Cannula in carotid, blood pres, 80		
4 15 p m	Cannula in main duct Secretion slight, blood pressure, 50			
Time	Pulse	Resp	Temp	Pan Flow
4 15-4 30				24
4 30-4 45				17
4 45-5 00				15
5 00 p m	Animal bled to death from the femoral artery			

Necropsy—The pancreas was just beginning to become pink in color. The vessels were slightly congested.

Series E—In this series of two experiments, after recording the normal flow of pancreatic juice, one adrenal was removed leaving the other intact. This procedure did not produce adrenal insufficiency, yet the increase in flow of pancreatic juice was just as great as in the instances in which both glands were removed. This fact is shown by the following experiment.

Experiment 11 (Series E) April 9, 1915. Adult male poodle dog. Weight, 8,200 grams. Was fasted for thirty-six hours prior to the operation. Pulse 130, respiration 24, temperature 101.2. Normal blood pressure 144. Etherized at 7 45 a m.

Time	Pulse	Resp	Temp	B P	Pan Flow
8 00 a m	142	36	101.0	144	
	Abdomen opened and the minor pancreatic duct ligated. Cannula placed in the main pancreatic duct.				
8 30-8 45					02
8 45 a m	160	28		116	
	Left adrenal removed				98
8 45-9 00 a m					025
9 00 a m	173	56	100.2		
9 00-9 15		..			04
9 15-9 30					03
9 30 a m	216	52	100.0		

Time	Pulse	Resp	Temp	B P	Pan Flow
9 30-9 45					05
9 45-10 00					06
10 00 a m	184	48	100 1		
10 00-10 15					06
10 15-10 30					10
10 30 a m	180	39	100 0		
10 30-10 45					15
10 45-11 00					20
11 00	240	42	99 8		
11 00-11-15					22
11 15-11 30					20
11 30 a m	240	54	104 0	85	
11 30-11 45					22
11 45-12 00					23
12 00	240	48	104 6	85	
12 00-12 15					23
12 15-12 30					30
12 30 p m	268	72	103 4	85	
12 30-12 45					36
12 45-1 00					42
1 00-1 15					58
1 15-1 30					60
1 30 p m	270	52	103 8	50	
1 30-1 45	Animal growing very weak			40	
1 45-2 00					1 15
2 00 p m	240	38	104 2		
2 00-2 15					89
2 16	Animal died				

Necropsy—Stomach almost empty, no free fluid, mucosa acid in reaction

Group 2—Method A The flow of pancreatic juice in unanesthetized animals was studied in one series of experiments. In three other series the condition of the gland itself was studied.

Series F—In this series of five experiments a temporary pancreatic fistula was established in an animal in which one adrenal had been removed. The fistula was made under sterile conditions by securely fixing a glass cannula in the major duct, after ligating the accessory duct. After observing the rate of pancreatic flow, and when the animal had recovered from the effects of the operation, the remaining adrenal was removed and the animal observed until death. These experiments were more or less unsatisfactory because of clotting of blood in the cannula, infection and necrosis of the duct at the point where the cannula was tied. In none of these experiments was there an increased flow of pancreatic juice after adrenalectomy, however, in none of the animals did the pancreas have the injected blood vessels and characteristic color as observed in the double adrenalectomized animal. The most important fact learned from these experiments was that the slight increase in flow noted in most of the anesthetized animals, after removal of the adrenals, was wholly insignificant when compared with the secretion of the gland during digestion. In the anesthetized animal the flow usually did not reach, and rarely exceeded, 0.05 c c in a quarter

of an hour, while in unanesthetized animals, of approximately the same size, during the digestive period the secretion was as much as 1 c c per minute. This fact is emphasized by the following experiment

Experiment 4 (Series F) White and brindle male bulldog, old, very prone to fight. Right adrenal removed at 10 a m, Oct 31, 1914. Wound kept in good condition. Nov 3, 1915, 10 a m, the accessory pancreatic duct was ligated and glass cannula placed in main duct. Moderate secretion. Temperature of kennel maintained at 70 F. The animal drank milk at 12 m.

Date	Time	Pulse	Resp	Temp	Pan Flow, c cm
11/3/15	2 15 p m	84	18	104.3	6.80
	5 00 p m	120	12	103.0	5.40
	6 10 p m	90	12	102.0	3.75
	6 15 p m	Animal drank milk			
	8 30 p m	90	12	102.0	3.75
11/4/15	6 15 a m	140	12	103.0	1.15
	9 00 a m				12.0
	9 30 a m	Remaining adrenal removed			
		of pancreatic juice after this time			
	11 00 a m	156	30	102.0	
	12 00 m	Animal drank milk			
	2 16 p m	210	24	102.2	
	5 30 p m	168	18	103.0	
	9 15 p m	240	12	103.0	
		Animal died during night			

Necropsy—The pancreas, aside from a slight congestion, seemed normal. Pancreatic cannula had ulcerated out of position.

Series G—In practically all experiments, in anesthetized and unanesthetized animals, the contents of the stomach were found at autopsy to be acid. That the characteristic appearance of the pancreas, after removal of the adrenals, is not dependent on the acid condition of the stomach is proved by the results of this series of experiments. In five animals sodium bicarbonate, in large doses, was administered by a stomach tube every few hours from the time the last adrenal was removed until death occurred. While it is impossible to state that alkaline reaction of the stomach contents was maintained, it is certain that very little acid reached the duodenum. At necropsy in these animals the pancreas presented the same characteristic appearance as in other adrenalectomized animals.

Experiment 5 (Series G)—Dog B169. Feb 12, 1915, right adrenal removed. Feb 22, 1915, at 10 45 a m the left gland was removed. Sodium bicarbonate in 5 gm doses was administered about every four hours until death on Feb 28, 1915, at 8 a m.

Necropsy—Pancreas very dark, mulberry color, blood vessels markedly injected.

Series H—In six experiments, after removing one adrenal the pancreatic ducts were doubly ligated and sectioned. At different times, varying from a few days to a few weeks, the remaining adrenal was removed. At autopsy of these animals the pancreas did not show the

characteristic color and injected blood vessels. In the experiments in which the last adrenal was removed shortly after ligation of the ducts the pancreas appeared normal, when a few weeks had elapsed between operations, the gland was converted into a hard, fibrous mass. The following experiment is an example.

Experiment 5 (Series H)—Dog B83. Small terrier about 8 months old. Nov. 10, 1914, at 11 a. m. both pancreatic ducts were ligated and right adrenal removed. At 4 p. m. seemed to have recovered from anesthetic and immediate effects of operation.

Nov. 11, 1915. Remaining adrenal was removed.

Nov. 12, 1915. Animal appeared normal.

Nov. 13, 1915. Developed the signs of adrenal insufficiency and died at 2 p. m.

Necropsy—Site of the operations in good condition. Pancreas normal color, lobules stand out prominently, vessels not injected, firm, duct ligatures holding.

In one series of five experiments after the removal of both adrenals and the development of the moribund condition of adrenal insufficiency, the animals were bled to death. At necropsy the blood vessels of the pancreas were found to be still markedly injected with blood.

METHOD B HISTOLOGIC CHANGES IN THE PANCREAS AFTER ADRENALECTOMY

Sections of the pancreas removed at necropsy from doubly adrenalectomized animals, when stained by the common methods, were rather characteristic. The islands were prominent, engorged with blood, and seemed more numerous than in sections from normal animals. The acinar tissue seemed to be decreased in amount. In order to study these changes to better advantage, the special differential stains of Bensley⁶ were used. After the careful study of many sections from different animals, the following facts were ascertained:

1. There is a marked congestion which appears like a hypostatic congestion. Every capillary seems filled with blood.

2. There is very little or no zymogen present. When zymogen is present, it is found in the acinar cells which surround the islands or the small blood vessels. This loss of zymogen seems proportionate to the length of time that the animal has been moribund, the greatest loss being found in those cases in which the specimens were secured an hour or so after death. If the gland was removed immediately after death, there was less zymogen than if the animal was bled to death a few hours before it would otherwise have died. This loss of zymogen seems to be more closely related to the decrease in blood pressure than to the rate of pancreatic secretion. Evidently the storage

⁶ Bensley. Studies on the Pancreas of the Guinea-Pig, *Am Jour Anat*, 1911-12, xii, 297.

function of the acinar cells was affected more by the decreased food supply than by secretion

3 The islands appear larger and more numerous than in sections from the normal animal. On close examination, after using Bensley's stains, some of these apparent islands were found to consist partially of island cells and partially of degenerated acinar cells. Some apparent islands were made up entirely of degenerated acinar cells.

4 The number and size of the islands, as well as the zymogen content, seem to depend on the length of time that the animal is moribund as well as on the length of time after death that the tissue is removed and fixed. Degenerative changes in the pancreas apparently occur slowly during the dying state and very quickly after death. The acinar cells show these changes before they appear in the island cells. The former lose their shape with the loss of zymogen, becoming more rectangular. The nucleus seems to move into the center of the cell. Both nucleus and cytoplasm stain much less intensely. Degeneration granules which take the acid stain appear in the protoplasm. All these changes make the acinar cells appear more like the island cells. As the changes proceed these groups of degenerated cells coalesce and a line of demarcation appears around them. The acini nearest the true islands seem most affected. They apparently join with the group of island cells to form a larger island. Isolated groups of these changed acinar cells increase the number of the apparent islands.

SUMMARY

The following facts may be taken to express a specific relationship between the adrenals and the pancreas.

1 The pancreas develops a characteristic pink color and its blood vessels are injected to a maximum degree after double adrenalectomy. This appearance is not dependent on the acid condition of the fluid in the stomach, but is probably associated with patent pancreatic ducts. The blood found in the injected pancreatic vessels cannot be removed by a free hemorrhage.

2 In an anesthetized animal the flow of pancreatic juice is always slightly increased after the removal of the adrenals.

3 There is a marked decrease in the zymogen content of the pancreas in adrenalectomized animals.

Against these data are the following.

1 The hyperemic condition of the pancreas does not take place until there is evidence that arterial tone is decreasing in the other organs.

2 The increased flow of pancreatic juice in the anesthetized animal after removal of the adrenals is but little greater than that which occurs in the normal anesthetized dog under the same conditions as regards blood pressure, etc , and it does not exceed the increase incident to the trauma from the removal of only one adrenal Further, the flow is insignificant as compared to the flow during the process of digestion In an unanesthetized animal, no increase in flow of pancreatic juice after removal of the adrenals is demonstrable

3 The decrease in zymogen content is proportional to the time of low blood pressure

4 All the changes found in the pancreas are proportionate to the length of time that the animal was in a moribund condition

From a comparison of these data it is seen that all the changes found in the pancreas grossly, histologically and functionally, after removal of the adrenals, can be accounted for by the changes in general taking place in the organism as a whole, due to decreased blood pressure, decreased temperature, and the other changes incident to the development of the moribund condition We have been unable to demonstrate any specific relationship between the adrenals and the pancreas

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CARBOHYDRATE UTILIZATION IN DIABETES

BASED ON STUDIES OF THE RESPIRATION, URINE AND BLOOD *

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In the classical work of Naunyn¹ on diabetes mellitus occurs the following passage "In general, even in severe diabetes, at least in man, the carbohydrates ingested are not completely excreted in the urine again as sugar. A portion of the starch, as well as of the dextrose, will be burned in the organism." This view was also shared by Kulz. Naunyn, however, refers to a case in which von Mering records an excretion of all the sugar ingested, and attention is called in the report of the cases of Kulz to four instances in which apparently a similar condition existed.

Von Noorden² defines diabetes as "a disease in which the capability of the organism adequately to burn grape sugar is pathologically lowered," and in another place³ he says "One cannot help thinking that, in man, even when death has resulted from coma, the diabetes has not always been 'quite complete'—that is to say, the pathological processes which produce diabetes have not developed so far, and the factors which favor the storing up of glycogen have not been so completely destroyed as is the case in a dog whose pancreas has been entirely ablated."

Notwithstanding all the work on diabetes, this question of the utilization of carbohydrates in human diabetes has not been settled. In diabetic dogs evidence has accumulated pointing to the complete loss

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* From the Nutrition Laboratory of the Carnegie Institution of Washington, Boston

* I wish to acknowledge my grateful appreciation of the help received from Mr Emmes, Miss Babcock, Miss Tompkins, Miss Coison and Miss Sandiford of the Nutrition Laboratory, as also my indebtedness to Mr Higgins, who controlled several of the experiments with the Tissot apparatus, and to my secretary, Miss Helen Leonard, for cheerful work on long computations and puzzling charts

1 Naunyn. *Der Diabetes Melitus*, 1906, p 173

2 Von Noorden. *Zuckerkrankheit*, Ed 6, 1912, p 2

3 Von Noorden. *Metabolism and Practical Medicine*, 1907, iii, 542

of this power to utilize carbohydrate, and the work of Murlin and Cramer⁴ has given definite results on this point, although so recent a writer as Landsberg,⁵ working from a different point of view with other animals, comes to the opposite conclusion. The present paper is concerned with diabetes in man and I wish to call attention to certain observations bearing on this problem which are related to the body weight, the urine, the storage of carbohydrate in the body, the respiratory metabolism of diabetics both fasting and following the administration of food and the remarkable disappearance of acidosis in diabetics with prolonged fasting, which is associated with a rise in their respiratory quotient.

I THE INFLUENCE OF WEIGHT ON THE DETERMINATION OF THE UTILIZATION OF CARBOHYDRATES IN DIABETES

The changes in weight which occur in a normal individual, following a slight increase of the carbohydrate in the diet, are so striking that one might hastily conclude that a study of the weights of a diabetic patient would give some idea as to his utilization of starch and sugar. A closer scrutiny of the problem, however, reveals many difficulties. In the first place, the diet employed in most cases of diabetes and all severe cases, is low in carbohydrates, and seldom reaches 10 per cent of that of normal individuals. In other words, it amounts to less than 50 gm carbohydrate—200 calories—per day. The effect of 200 calories on the weight is possible of determination theoretically, but practically such an experiment is difficult because the protein, fat and carbohydrate must be kept at uniform levels for a long period. But in a severe case of diabetes some of even this small amount is lost in the urine, which renders the available carbohydrate for increasing the weight still less. There are other complications. In a severe case of diabetes, the patient with 50 gm of carbohydrate in the diet, usually excretes more than 50 gm of sugar in the urine, and it is difficult to assign in proper proportion this excess of urinary sugar between the carbohydrate ingested and the carbohydrate already stored in the body on the one hand, and the protein simultaneously ingested and the body protein on the other.

Remarkable changes in the weight of normal as well as of diabetic patients will also occur, although the caloric value of the diet remains constant, if the proportion of fat to carbohydrate is altered. A diet rich in carbohydrate brings about an increase in weight, whereas a diet of exactly the same number of calories, although chiefly made up of fat, lowers the weight. These changes undoubtedly are due simply

4 Murlin and Cramer Jour Biol Chem, 1913, xv, 365

5 Landsberg Deutsch Arch f klin Med, 1914, cxv, 465

to the retention of water by the tissues on a carbohydrate diet, and loss of water on a fat diet. Such changes appear reasonable because the storage of 1 gm of carbohydrate in the body demands the retention of 3 gm of water, 1 gm of protein requires the storage of 0.75 gm of water, and 1 gm of fat requires only 0.1 gm of water. These changes are well illustrated⁶ by Table 1.

TABLE 1—CHANGES IN WEIGHT UNDER FAT AND CARBOHYDRATE DIETS

Date	Food and Drink			Body Weight kilos	Gain (+) or Loss (—) gm
	Solid Matter gm	Water gm	Total gm		
4/16/04				75.086	
4/16-17/04	970	3,577	4,547	75.443	+ 357
4/17-18/04	966	3,553	4,519	75.114	— 29
4/18-19/04	966	3,491	4,457	75.269	— 145
FAT DIET					
4/19-20/04	750	3,108	3,859	74.319	— 950
4/20-21/04	745	4,150	4,896	73.480	— 839
4/21-22/04	747	4,152	4,899	72.528	— 952

Average gain per day, carbohydrate diet, + 61 gm

Average loss per day, fat diet, — 914 gm

Water stored per day, carbohydrate period, + 165 gm

Water lost per day, fat period, — 906 gm

It is important for the clinician to bear this in mind, because it explains the rapid change in weight which often follows the initial diminution of the carbohydrate in the diet of diabetic patients and its replacement with fat.

An increase in weight following a marked increase of carbohydrate in the diet is strikingly illustrated in severe diabetic patients under the oatmeal treatment.⁷ Under these conditions the weight may rise 4.5 kg in one or two days. Undoubtedly you all have seen edema during the course of an oatmeal cure. It is significant that some of these cases show little or no carbohydrate in the urine. I cannot give proof that patients showing this increase in weight fail to give evidence of burning more than a trifling amount of carbohydrate, but from other similar cases I suspect this often to be the case. This point deserves further study. I think, however, that there will be general agreement that the gain in weight following the sudden introduction of large quantities of carbohydrate is accounted for by the storage—temporarily, perhaps—of carbohydrate in the body. That this storage or delay of excretion is accentuated in the presence of diseased kidneys

6 Benedict and Joslin. A Study of Metabolism in Severe Diabetes, Carnegie Institute of Washington, 1912, Pub No 176, p 93

7 Mirowsky. Deutsch med Wchnschr, 1912, xxxviii, 459

is common knowledge Barrenscheen⁸ showed that milk sugar excretion was delayed on the day following an oatmeal cure

The administration of sodium bicarbonate is frequently followed by a gain in weight Thus,⁹ in Case 220, the changes in weight during the administration of sodium bicarbonate were as shown in Table 2

TABLE 2—CHANGES IN WEIGHT DURING THE ADMINISTRATION OF SODIUM BICARBONATE

Date	Sodium Bicarbonate gm	Body Weight kilos	Date	Sodium Bicarbonate gm	Body Weight kilos
11/2	0	48.1	11/7	20	50.7
11/3	0	48.6	11/8	20	51.5
11/4	0	49.0	11/9	20	52.4
11/5	0	48.6	11/10	20	53.3
11/6	20	49.3	11/11	20	53.3

In order to show that this gain in weight was not directly due to the alkali, but rather to retention of salt, the weights of another diabetic patient, Case 135, were taken while on a salt-free diet¹⁰ (Table 3)

TABLE 3—CHANGES IN WEIGHT ON A SALT-FREE DIET

Intake							Urine								
Date, 1908	NaHCO ₃ Gm	Carb, Gm	Protein, Gm	Fat, Gm	Alcohol, Gm	Liquids cc	Vol, cc	N, Gm	NH ₃ , Gm	Acetone and Diacetic Acid, Gm	Beta oxy Acid, Gm	P ₂ O ₅ , Gm	Ol, Gm	Sugar, Gm	Wt, Lbs
1/26	0	135	110	185		3,500	3,720	21.8	4.2	7.9	29	4.4	8.2	160	88¼
1/27	0	135	110	185		3,500	3,940	19.6	4.3	7.8	29	4.5	6.3	165	89¼
1/28	0	135	110	185		3,500	3,210	20.5	4.4	7.3	24	4.6	5.9	160	86¾
1/29	0	135	90	155		3,500	3,210	19.2	4.1	7.3	26	4.2	4.8	163	85¾
1/30	25	135	70	185		3,500	3,190	16.3	3.5	8.7	33	4.1	1.6	146	85
1/31	25	120	60	95	23	5,370	4,600	19.1	4.3	12.6	51	5.1	2.3	146	83¼
2/1	37	130	100	130	45	5,250	4,050	18.7	3.3	10.7	39	4.3	2.0	137	82¼
2/2	52	70	60	95	45	5,370	3,510	16.0	3.5	10.2	37	3.9	2.1	121	81¾
2/3		15	15	30	45	800	360	15.0						86	

It will be seen that while on the salt-free diet the weight steadily fell, and despite the administration of sodium bicarbonate later, no increase in weight occurred. This observation has been elsewhere confirmed. I might here make the clinical observation that a salt-free diet in diabetes is inadvisable. It is also interesting that I have never

⁸ Barrenscheen. *Biochem Ztschr*, 1912, xxix, 232

⁹ Benedict and Joslin. *Loc cit* (Note 6) p 94

¹⁰ Joslin and Goodall. *Jour Am Med Assn*, 1908, li, 727

seen the death from diabetic coma of a diabetic patient who had dropsy, nor have I encountered such in the literature

The simple enumeration of these various facts affecting the weight shows how complicated is the determination of the utilization of carbohydrate from it alone. Changes in weight, however, do afford, when combined with other methods of clinical investigation, new fields for work

The changes in weight which a healthy fasting man undergoes at the beginning of a fast are known. The fasting man at the Nutrition Laboratory lost 2,850 gm in three days, and consumed during these three days body substance equivalent to 161 gm of protein, 149 gm of carbohydrate and 407 gm of fat. It is possible that from a series of observations on diabetic patients similarly fasted, conclusions of value as to the storage of carbohydrate in the body might be secured. Ten of my patients who were available for this purpose showed on an initial fast a loss of weight considerably less, and occasionally a gain in weight was recorded. Following the termination of the fast, although very little food was given, an increase in weight out of proportion to the amount of food given was almost invariably observed.

In one case no mineral waters or alkalis were taken, and yet gain in weight occurred during fasting. It is not unexpected that the gain in weight was often coincident with a fall in the excretion of urine. A gain in weight during fasting raises the question as to whether new carbohydrate has not been formed in the body, and as a result of its formation water retained. This line of investigation deserves attention. It will be referred to later in the discussion of severe cases of diabetes treated by prolonged fasting, the method which Dr F M Allen¹¹ has had the courage to introduce and has so accurately defined that it is safe for any practitioner to employ.

II THE UTILIZATION OF CARBOHYDRATES BASED ON INTAKE IN DIET AND OUTGO IN URINE

The comparison between the carbohydrate ingested and the sugar excreted in the urine is the common method of determining the utilization of carbohydrates. It would appear to be a simple procedure, but, as a matter of fact, the problem is far more difficult than has heretofore been considered. Your attention is first directed to the possibilities of error in reckoning the carbohydrate in the diet. Most severe diabetics under careful observation live on diets low in carbohydrate, seldom in excess of 50 gm. Therefore errors of 5 gm in the estimation of

¹¹ Allen Jour Am Med Assn, 1914, lxiii, 939, Boston Med and Surg. Jour, 1915, clxxv, 241

carbohydrates, though actually small, are proportionately large. It is seldom that the actual quantity of carbohydrate in the diet has been analyzed. In many of the cases food has not even been carefully weighed, and approximate portions of food have been supposed to contain definite quantities of carbohydrate. Take, for example, cream. The quantity of carbohydrate contained in half a pint may vary 5 gm, making an error of 10 per cent, if the total carbohydrate for the day amounted to 50 gm, or 20 per cent if limited to 25 grams.

Vegetables constitute a considerable proportion of the diet of these patients with severe diabetes. Often in the literature—and I plead guilty to the charge—the quantity of carbohydrate in the mixture of vegetables chosen from those containing less than 10 per cent carbohydrate for the day, has been roughly estimated. Recently I have taken more careful account of the amount of vegetables eaten, and it has come out that the quantity of vegetables prescribed and eaten frequently varies from 300 gm to 1,000 gm. Any accurate computation, therefore, of a carbohydrate balance must be based not alone on the total quantity of vegetables eaten in the day, but on the actual quantity of each vegetable, even in these low carbohydrate groups. Furthermore, varieties of the same vegetable vary in percentage of carbohydrate. It makes a difference of 5 gm in a day whether 500 gm vegetables contain 1 per cent more or less of carbohydrate. But this is not all. Analyses of carbohydrate in vegetables include the cellulose contained in them as well as the starch and sugar. How much shall we subtract from our total carbohydrate intake on account of this undigested cellulose which is lost in the feces?

The other foods commonly used in the study of the metabolism of diabetic patients are potato, oatmeal, bread, fruit. The potato, oatmeal and bread are usually carefully weighed, and the analyses of these foods are fairly constant, but the percentage of carbohydrate is so large that I should not dare to be positive about the quantity of carbohydrate which my patient received unless standard varieties of these foods were employed. With fruit frequent errors exist, because usually an orange or grapefruit is allowed and seldom the actual weights of the portions eaten are determined. A further error occurs in that the intake of carbohydrate is reckoned indifferently as starch or sugar. As a matter of fact, 100 gm of starch when converted to sugar amount to 105 gm. Errors of 5 and 10 gm a day in computing the carbohydrate intake may easily occur and in a period of a week form notable amounts, from 35 to 70 gm. Physiologists and physicians must not take too seriously clinical statements about the carbohydrate in the diet, and greater accuracy must be employed in the future. We need, first, a standard test diabetic diet, and, second, we need to

employ it for at least five days. Unfortunately, even at the end of this time the results may be unsatisfactory, because the condition of the patient's tolerance may have changed in this period either for better or worse.

The estimation of sugar in the urine is far more accurate than that of the carbohydrate in the diet, provided the analysis is made in one of our best laboratories, but I would hesitate to accept as final in accurate computations many routine analyses made in private practice or in hospitals. Too often the method employed in the estimation of the sugar is not mentioned, and I suspect many results are obtained with the polariscope which may involve an error of 20 gm or more, owing to the presence of levorotary bodies. Urinary analyses, however, are usually far and away ahead in accuracy of that observed in the collection and measurement of the urines of diabetic patients. The admirable methods adopted in the ward of the Russell Sage Institute at Bellevue Hospital and at the Rockefeller Hospital have been seldom followed by experimenters in the past. I pass over errors of forgetfulness or design on the part of the patients, as regards both diet and collection of urine. Dogs may not be any more honest, but we do not expose them to temptation or trust their memory. How often a patient states that a trifling amount of urine has been lost at stool! I realize this is trite, but a good share of the arguments based on the utilization of carbohydrate rests on data which are not above reproach.

The variability of excretion of urine and urinary constituents from day to day is another source of error. If the diet is not constant the variation may be great. In one of our tests designed to determine the utilization of levulose, during seven days prior to the administration of levulose the average volume of urine was 1,079 c c. On the day the levulose was given the volume of urine was 966 c c, the next day 390 c c, and on the following day it amounted to 1,175 c c, it then returned to near the average quantity. Yet the habits of this patient's daily life were nearly constant, and except for the one levulose day changes in the diet were not extreme. Such marked variations in the volume of the urine on successive days must be reckoned with, because with such great changes in volumes of urine, the quantities of the constituents of the urine change too, though to a much less extent. In this same case, the average daily excretion of nitrogen for the fifty-five days which included this period was 7.3 gm, but on the day when 81 gm levulose were given with very little other food, it fell to 6.53 gm and on the next day to 4.34 gm. This low point was never reached by this same patient on a fasting day, and the quantity of levulose is considerably less than would be supposed to exert so strong a positive action, particularly when delayed or diminished oxidation

is taken into consideration Consult Table 4 and also chart of variations in excretion of urine and sugar of a severe diabetic on a constant diet, shown further on

TABLE 4—EFFECT OF LEVULOSE

Case 785 Male, aged 17 Weight, 42 Kilos

Output					Intake				
Vol, cc	Diac Acid	Sugar, Gm	Nitrogen, Gm	Ammonia, Gm	Carb, Gm	Prot, Gm	Fat, Gm	Alcohol, Gm	Calories
1,079*	+	11 1†	7 83		17	58	127	9	1,506
966	+	7	6 53	0 69	90†	21	30±	3	735
390	++	5	4 34	0 35	20	63	110	9	1,385
1,175	+	3	8 35	0 74	20±	63	110±	9	1,385±

* Average for previous seven days

† None on six days

‡ Levulose, 81 gm Carb in Diet 9 ± gm in the form of vegetables

Experiments designed to test the utilization of carbohydrate should be conducted on patients who are in equilibrium both as regards weight and urinary excretion

III THE IMPORTANCE AS WELL AS THE INFLUENCE OF CARBOHYDRATE STORED IN THE BODY ON THE UTILIZATION OF CARBOHYDRATE INGESTED

It is well known that following a period of fasting large quantities of carbohydrate can be administered without subsequently appearing in the urine The best illustration of this is von Noorden's oatmeal treatment Thus Case R of the Benedict and Joslin series¹² showed a positive carbohydrate balance of 520 gm during an oatmeal cure, although he never after this cure became sugar-free save for occasional days, despite rigorous dieting A more spectacular demonstration is the severe diabetic of Klemperer,¹³ who took 100 gm of glucose in divided portions during twenty-four hours without more than a few grams appearing in the urine Almost as striking is that of a boy of 17 (Case 785) who came to me in the twentieth month of the disease By consulting Table 4 it will be seen that only 7 gm of sugar appeared in the urine following an intake at one time of 81 gm levulose, although by observations before and after the tolerance was known to be low A summary of his metabolism is given in Table 5

12 Benedict and Joslin Loc cit (Note 6) p 57

13 Klemperer Therap d Gegenw, 1911, 11, 447

TABLE 5—SUMMARY OF METABOLISM IN CASE SHOWN IN TABLE 4*

Case 785 Severe diabetes. Weight, 42 kilos Male Age at onset, 15
Duration since onset twenty months

Period	Nitrogen Balance		Carbohydrate Balance	
	Urine and Feces	Diet	Urine	Diet
55 days	440	407	190	919
Daily average	8 0	7 0	3 5	16 7
Daily average	8 9	Sugar present in urine 20 days		15 4
		7 8	8 8	
Daily average	7 5	Sugar absent from urine 32 days		15 1
		6 4	0 0	

* Nitrogen in feces estimated at 10 per cent of nitrogen in diet

During the fifty-five days he was under my observation the average daily nitrogen in the diet was estimated at 7 0 gm, and in the urine and feces 8 0 gm. The carbohydrate in the diet was 16 7 gm and in the urine 3 5 gm. During thirty-two of the fifty-five days, sugar was absent from the urine and on twenty days it was present, although the average daily carbohydrate in the diet was the same. A study of Table 5 would suggest this being due to the slightly lower nitrogen intake on the sugar-free days. This is not quite justifiable, because another factor enters in—namely, starvation—for on several of the thirty-two days the patient received no food at all. These starvation days evidently played an important rôle. How very important is shown by the test already recorded in Table 4, where 81 gm of levulose were administered and only 7 gm carbohydrate appeared in the urine.

Is it possible for the body to store so large a quantity of carbohydrate as 520 or even more grams? Furthermore in what form may it be retained in diabetic patients?

Nearly all experiments on the utilization of carbohydrates in the past have been based on the difference between the carbohydrate intake and the carbohydrate excreted. Unless the amount of the carbohydrate stored in the body is known, it is unjustifiable to say that the carbohydrate excreted represents a part of that ingested during the same twenty-four hours. All data in reference to the D N ratio are confused by the possibility of stored carbohydrate. The importance of the storage of carbohydrate thus becomes evident.

The influence of carbohydrate so stored in the body is also great. Whatever virtue the oatmeal cure possesses, all agree that it depends

in major part on preceding starvation, which has tended to exhaust the carbohydrate depots of the body

Glycogen —Carbohydrate is stored in the body in various ways but most of it is supposed to be in the form of glycogen, and this is about equally divided between the liver and the muscles. An old estimate of Bunge that the body had 400 gm is roughly approximated by experiments on fasting men and professional athletes doing severe work without food. This figure may be taken as a fair average, but there are enormous variations. This statement is based on glycogen which has been shown to be burned, it does not exclude the possibility of some glycogen still remaining in the body, and in fact Benedict says "It would appear that the estimate of 400 gm of glycogen for the content of the body is if anything too small rather than too large." Experiments on fasting men show that they may burn from 93 to 232 gm in the first three days^{14, 15}. In diabetic patients the quantity of glycogen is universally considered to be far below this amount, but Frerichs¹⁶ found, on puncturing the liver of two diabetics, a small amount of glycogen in one and a considerable amount in the other, and Kulz¹⁷ found from 10 to 12 gm glycogen in the liver of a diabetic who had been for a long time on a diabetic diet. Examinations of the tissue removed from the livers of living diabetic patients show appreciable quantities of glycogen, and it is the experience of pathologists that the organs of diabetic patients contain more than traces of glycogen. It is most unfortunate that no data exist which enable us to determine what this minimum is. It is quite conceivable that although it might be extremely small at any one moment, a small quantity might be frequently formed and destroyed, and the sum of these small quantities reach a substantial amount in twenty-four hours.

The recent work of Helly¹⁸ throws new light on the problem. He points out the striking contrast between the constant presence of glycogen in the liver of human diabetes and the very small quantity which is found in the severe diabetes of depancreatized dogs, yet even in the latter the power of the liver to form or deposit glycogen is shown when levulose is administered. If a milder form of diabetes is produced in the dog more glycogen remains in the body and there is a closer resemblance to human diabetes, whereas with total removal of the pancreas there was only 0.065 per cent of glycogen in the liver.

14 Benedict. The Influence of Inanition on Metabolism, Carnegie Institute of Washington, 1907, Pub 77, p 464

15 Benedict. A Study of Prolonged Fasting, Carnegie Institute of Washington, 1915, Pub 203, p 251

16 Frerichs. Ueber den Diabetes, p 272, cited by Nehring and Schmoll (Note 34)

17 Kulz. Arch f d ges Physiol (Pfluger's), 1876, LIII, 267

18 Helly. Ztschr f exper Path u Therap, 1914, xv, 464

On the other hand, with partial removal, even though there be 8 to 10 per cent of sugar in the urine, there was 0.3 per cent. of glycogen. By microscopic examination so considerable a quantity as this appeared small.

Blood Sugar—Sugar is also stored in the body in the form of blood sugar. The normal quantity of sugar in the blood of healthy individuals varies between 0.07 and 0.11 per cent and for convenience in calculations may be considered 0.1 per cent. This rises quickly after a meal rich in carbohydrates, but soon falls to its former level. In fifty-five observations on fifteen of our diabetic patients the percentage of blood sugar varied from 0.12 to 0.36 per cent. But the blood of these diabetic patients does not behave like that of normal individuals following the ingestion of food. It is true that the percentage of sugar rapidly increases following a carbohydrate meal, but it does not as rapidly fall, and in my own experience most diabetic patients, even after prolonged fasting, show values for blood sugar which are far above normal. Certain types of diabetic patients—namely, those with disease of the kidneys—are especially prone to maintain high percentages of sugar in the blood for many days after their urines have become sugar-free. It is impracticable to consider that the percentage of blood sugar is maintained independently of the other tissues in the body—first, because the percentage is so unstable, second, because there is no constant relation between the sugar in the blood serum and the sugar in the total blood, and third, because the capacity of the blood for storage of sugar is so slight. If we assume an individual of 70 kilos body weight and consider that 7 per cent of the weight is made up of blood, we have 4.9 kilos of blood with a normal sugar content of 0.1 per cent. This would amount to 4.9 gm, even taking the highest for the normal individual and should we take the highest figures we have encountered even after the administration of food with our diabetic patients, namely 0.36 per cent, the total quantity of sugar stored in the blood would not be far from 18 gm—a trifle more than a half ounce.

Falta¹⁹ has called attention to the slow return of the blood of diabetic patients to its former sugar level, and emphasizes this point as of fundamental importance in diabetes. He points out that the disturbance of blood sugar utilization is not the same as the disturbance of glycogen formation for the blood sugar regulation may be interfered with when the glycogen formation is not.

Kleiner and Meltzer²⁰ have also beautifully shown this same difference in depancreatized dogs. Whereas, following the injection of

19 Falta Med Klin, 1914, x, 9

20 Kleiner and Meltzer Proc Soc for Exper Biol and Med, 1914, xii, 58

4 gm dextrose per kilo weight, the sugar in the blood of normal dogs increases fourfold—namely, from 0.20 per cent, to 0.79 per cent—and that of depancreatized dogs threefold—from 0.38 per cent before to 1.19 per cent after the injection—the blood sugar of the former returned nearly to normal at the end of an hour and a half, while the diabetic dogs even then showed 0.86. It is significant that in these experiments the quantities of sugar excreted in the urine were practically the same. Interesting as these figures are from this point of view, from another they are still more interesting. It is impossible to account for all the sugar ingested by adding together the sugar found in the blood and that in the urine. Where did the sugar go? You may say it was burned, and this possibility, though not probability, must be admitted in the normal animal, but no one would contend this to be wholly the case in the depancreatized animal.

At the Nutrition Laboratory we have been able to carry these experiments to their logical conclusion, for we have had the opportunity to determine the respiratory quotient following the administration of levulose to severe diabetics. In Table 20 will be found a report of the effect of levulose when administered to severe diabetic patients in amounts of 2.51 gm, 2.42 gm and 1.95 gm per kilogram body weight. In the first and third cases there was no increase in the respiratory quotient. A considerable portion of the levulose was probably excreted in the first case, but in the third little or none. The explanation of this difference in behavior in the storage of levulose is probably that the first patient had not fasted beforehand and that the third had been on a low carbohydrate diet for a long time, this is confirmed by the second case, in which also little of the levulose was excreted when administered following a period of strict dieting. An increase in the respiratory quotient occurred in this case, but it was so slight as to preclude any considerable quantity of the sugar having been burned. It should also be recorded that in all the cases the levulose was given at one time and not spread out through the twenty-four hours, as in Klemperer's test. This gives added emphasis to the possibility of the presence of an empty storehouse for carbohydrate in the body. I also have evidence that the gradual administration of carbohydrates is of little value, provided the body is not prepared to retain it. Following etherization a patient (Case 808), while fasting for the first twenty-four hours was sugar-free, but on the next day, although only 2 gm carbohydrate per hour were administered, he excreted practically all of it, although formerly his tolerance amounted to 50 gm carbohydrate.

The small amount of glycogen and the still smaller quantity of blood sugar represent an amount of carbohydrate far too low to

account for the phenomena above described in diabetes. Other sources for storage of sugar in the body must be sought, as has been emphasized by Ivar Bang. If we should assume that the percentage of sugar in the blood was the same for all the fluid in the body, certain amounts of sugar might be stored in this manner. While such an assumption is not wholly justifiable, it has some basis, for we know that sugar exists in the spinal fluid of diabetics, as well as in other fluids. In normals Dr. Jacobson tells me that he has not found it so closely to follow the blood, but the opposite was true in his cases of diabetes mellitus. It gets into the blood and cannot seem to get out. Notable percentages of sugar, not very different from those in the blood, have been found in pleuritic and ascitic fluids, and Husband found even 0.7 per cent in the amniotic fluid. There is some doubt about its presence in sweat, but we do have a record of sweet tears. Yet granted that the assumption is correct, we cannot increase our storage capacity very much that way. For example, assuming the total quantity of fluid in the body as 60 per cent of the body weight of 70 kg, we have 42 kg of body fluid, from which we must deduct 4.9 kg already reckoned as blood. This leaves us a remainder of 37.1 kg of fluid in the body, and using the highest figure—0.36 per cent—for blood sugar which we have encountered, the quantity of sugar in this mass of fluid would be only 133 gm. This is not enough relatively to explain Kleiner's and Meltzer's experiment.

Another source for the formation, although perhaps not for the storage of carbohydrate in the body, has long been recognized in protein. The close connection which is maintained between protein and carbohydrate in diabetes would make a clinician with modest chemical knowledge seek for some combination of carbohydrate in the protein molecule—some arrangement by which a portion of the sugar molecule could be stored in protein or given up as occasion arises, just as water is squeezed out of a sponge. Good chemists, and I have asked many, assure me that even with glucoproteins sugar can be extracted from the protein molecule only when the molecule itself is disintegrated. The large quantity of movable protein and fat in the body suggests a large carbohydrate reservoir, too. Few realize how large this quantity of movable protein is. It has been shown by Albert Muller²¹ that by overfeeding, 210 gm of nitrogen, the equivalent of 1260 gm of body protein, in turn the equivalent of 6.3 kilos of muscle tissue, can be retained by the body, and conversely, it has been shown by Benedict¹⁵ that even more—277 gm—can be removed. This movable protein amounts to about one-third of the total body protein. The readiness

²¹ Muller Zentralbl f d Ges Physiol u Path d Stoffwechs, 1911, vi, 617

with which fat can be increased and decreased in the body is universally recognized

Although we are not allowed to say that carbohydrate can be extracted from the protein molecule, leaving it intact, we do know that in severe diabetes sugar can be formed out of protein. Professor Lusk²² has demonstrated this in completely depancreatized dogs and in his now famous diabetic patient, 3.65 gm dextrose appeared in the urine for each gram of nitrogen therein contained. This represents approximately 60 gm dextrose for each 100 gm protein. If we should assume that in diabetic patients there were 1,200 gm movable protein, this would furnish a possible source of 720 gm more of carbohydrate.

Unfortunately one cannot be sure that in the disintegration of the protein molecule the nitrogen and carbohydrate leave the body hand in hand. As a rule, the nitrogen lingers behind, greatly to our annoyance in estimating the source of the sugar in the urine. Mendel and Lewis²³ have recently shown that this delay was increased if either indigestible substances or cotton seed oil form a prominent part of the diet—just the sort of foods which our diabetic patients eat. Consequently if an attempt to determine the quantity of carbohydrate from protein (dextrose nitrogen ratio D/N) is made, this irregularity in the excretion of nitrogen must be considered. When one adds to this difficulty that of determining what share the quantity of residual carbohydrate in the body bears to the total sugar excreted, and when one considers that even under an absolutely uniform diet of 1,000 gm meat and 1,750 cc fluid intake for fifteen days Naunyn²⁴ found variation of sugar excretion from 12 gm to 43 gm, and frequently of 100 per cent, I feel very modest about asserting that my patients are producing any given quantity of sugar for each gram of nitrogen excreted. Naunyn says that these spontaneous variations may reach even 70 gm. Kulz has emphasized this same point. If under ideal conditions for fifteen days such variations exist, it behooves one to accept with caution reported D/N ratios for a period of a few days as being of value or to base arguments, as is sometimes done, on the D/N ratio of single isolated days selected from a series. In the tables of Rumpf, Allard, Hesse, and some of Luthje's, D/N ratios are recorded which Professor Lusk and I would feel indicated a far larger per cent of carbohydrate coming from protein than is actually the case. It is arbitrary selection to pick from these tables all ratios above 3.65/1 and say they are wrong and to class the remainder as correct. It is

22 Mandel and Lusk. *Deutsch Arch f klin Med*, 1904, lxxxii, 472

23 Mendel and Lewis. *Jour Biol Chem*, 1913-14, xvi, pp 19, 37

24 Naunyn. *Des Diabetes Melitus*, 1906, p 183

furthermore remarkable that with fasting all D N ratios cease to exist. It is also hard to understand how a patient one day fails to burn the protein of an ox, but the next day burns his own body protein with ease. Fasting diabetics will afford unusual opportunities to study this point. As a rule, the high D N ratios are found when the nitrogen excretion is high, and it may be that to produce these high ratios large quantities of protein may be required.

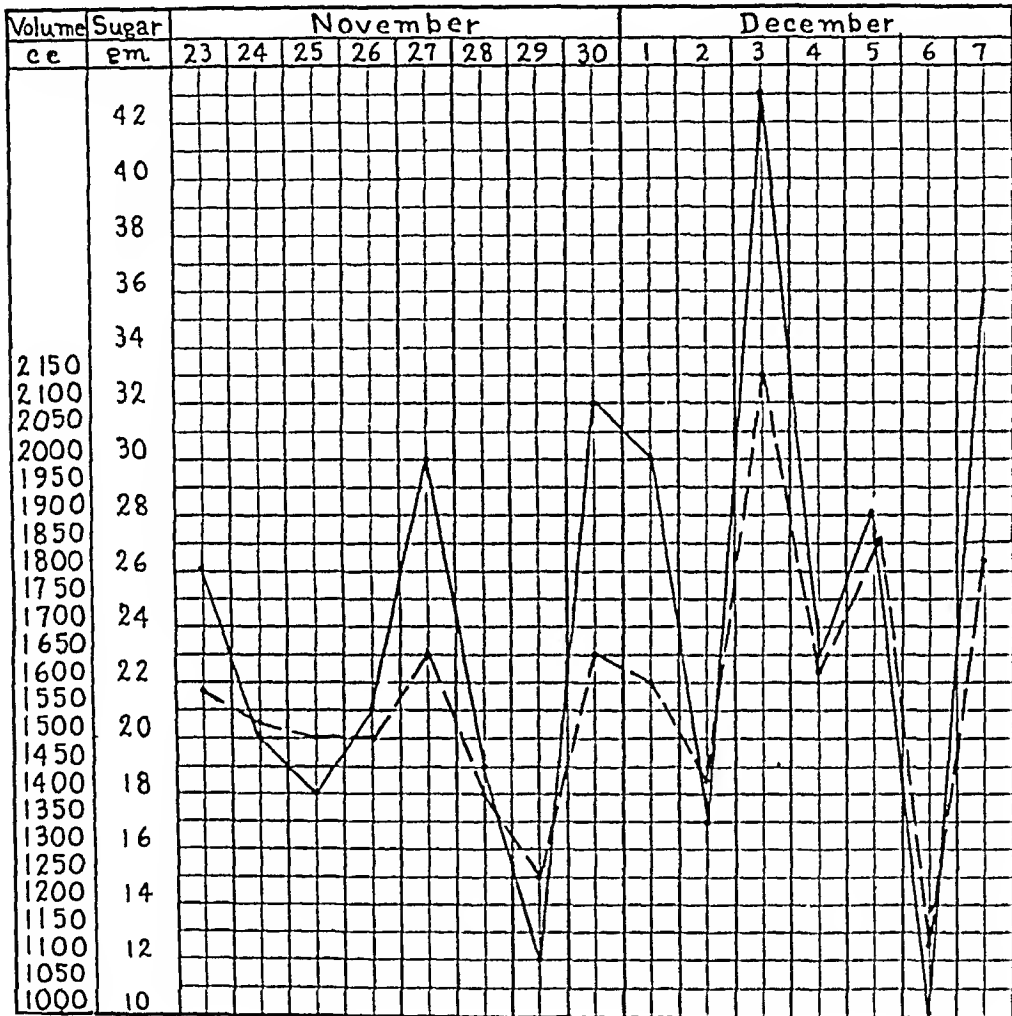


Chart illustrating variations in excretions of urine and sugar of a severe diabetic on a constant diet (from Naunyn). Diet constant 1,000 gm meat, 1,750 c.c. fluid. Line composed of dots and dashes indicates c.c. urine in twenty-four hours, continuous line, gm sugar in twenty-four hours.

The small part which the blood plays in the storage of carbohydrate has been pointed out. This is peculiarly unfortunate because one would hope from the percentage of sugar in the blood to derive some knowledge of the course of metabolism in diabetes. As if to emphasize the independence of the metabolism to the content of sugar in the body, I submit at this point Table 6, which gives the respiratory quotients obtained upon individuals whose blood sugar was deter-

mined at the time of the test, reserving discussion of the same to a later portion of the paper

TABLE 6—THE BLOOD SUGAR AND RESPIRATORY QUOTIENT IN SEVERE DIABETES

Case No	Condition	Per cent of Sugar in Blood	R Q
806	Fasting	0 12	0 71
806	Fasting	0 14	0 68
786	Fasting	0 17	0 69
806	After potato (60 gm carb)	0 18	0 69
765	Fasting	0 18	0 74
810	Fasting	0 19	0 72
806	After one egg and 200 gm vegetables	0 19	0 72
765	Fasting	0 23	0 76
765	Fasting	0 24	0 73
714	Fasting	0 25	0 78
786	After oatmeal (60 gm carb)	0 25	0 74
765	After oatmeal (10 gm carb) and potato (48 gm carb)	0 26	0 74
773	Fasting	0 27	0 70
773	After oatmeal (80 gm carb)	0 30	0 70
746	Fasting	0 30	0 70
746	After oatmeal (40 60 gm carb)	0 36	0 74
786	After oatmeal (120 \pm gm carb)	0 36	0 83

IV THE RESPIRATORY METABOLISM AND ITS RELATION TO THE UTILIZATION OF CARBOHYDRATE

An examination of the composition of the carbohydrate molecule will show that it contains sufficient oxygen to unite with all the hydrogen present. Consequently, for each volume of oxygen used in the oxidation of carbohydrate a volume of carbon dioxide will be produced. The relation which the volume of carbon dioxide produced bears to the oxygen required for the oxidation of a food constitutes its respiratory quotient. It is obvious, therefore, that the respiratory quotient of such a carbohydrate as glucose ($C_6H_{12}O_6$) is 1. It matters not whether the oxidation takes place rapidly outside of the body in a flame, or less obtrusively in the body during twenty-four hours. Protein, on the other hand, does not contain sufficient oxygen for the hydrogen atoms contained in its molecule. As a result, in the burning of protein, oxygen must be used not only for the carbon in the molecule, but for the hydrogen as well. The denominator of the fraction is thus increased, and the respiratory quotient of protein must be less than 1, and is 0.81. The protein molecule is made up of many component parts and while the respiratory quotients of these parts vary greatly, yet for protein as a whole the foregoing quotient, 0.81, holds. With fat a similar condition exists to that in protein, only there is still more hydrogen present to require oxygen, so that the amount of oxygen necessary for the combustion of fat is still greater, and as a result the respiratory quotient falls to 0.70. The respiratory quotient of alcohol is still lower, namely, 0.67. Beta-oxybutyric acid, which can be taken

as the chief one of the group of acid bodies formed in diabetes, has a respiratory quotient of 0.89, diacetic acid has a respiratory quotient of 1.00, and acetone of 0.75, so that one will not go far astray to take 0.89 as a common respiratory quotient for these three acid bodies.

The respiratory quotient of an individual can be determined by measurement of the quantity of carbon dioxide exhaled and the oxygen absorbed. When this is done, information is obtained concerning the character and total amount of the combustion taking place in the body. Since the urinary nitrogen gives us a definite idea of the quantity of protein metabolized, if we calculate what this represents and subtract it from the total material burned, we have left the combustion derived simply from fat and carbohydrate. When the respiratory quotient of fat and carbohydrate, as well as that of the individual, is known, it is possible, by computation, to determine the share which these two variables have taken in the total metabolism.

TABLE 7—THE RESPIRATORY QUOTIENT (R. Q.) OF A FOOD IS OBTAINED BY DIVIDING THE VOLUME OF CARBON DIOXID PRODUCED DURING ITS OXIDIZATION BY THE VOLUME OF OXYGEN ABSORBED

VOLUME OF OXYGEN ABSORBED	R. Q.
<i>Carbohydrate</i> $C_6H_{12}O_6 + 6 O_2 = 6 CO_2 + 6 H_2O$ Oxygen is required for oxidation of carbon alone 6 CO_2 produced 6 O_2 absorbed =	1.00
<i>Fat</i> $C_{55}H_{101}O_6$	0.71
Oxygen required for carbon and a large quantity of hydrogen	0.81
<i>Protein</i> Occupies an intermediate position	0.67
<i>Alcohol</i> C_2H_6O	0.89
<i>Beta Oxibutyric acid</i> $C_4H_8O_3$	1.00
<i>Diacetic acid</i> $C_4H_6O_3$	0.75
<i>Acetone</i> C_3H_6O	

The Technic of the Determination of the Exchange of Carbon Dioxid and Oxygen in Man—Two types of apparatus are employed to learn the exchange of carbon dioxide and oxygen in man, the calorimeter and respiration apparatus. In the closed chamber of the calorimeter the oxygen admitted and the carbon dioxide withdrawn can be accurately determined in periods usually of one hour's duration, but it is better to take the average of the results obtained in three successive periods. Occasionally each period may be shortened to three-quarters of an hour, exceptionally to half an hour, but the large size of the calorimeter increases the chances for error. The calorimeter is cumbersome, expensive to construct and to maintain, and the length of the experiment is not only disagreeable to the patient, but disadvantageous in studying the results of rapid changes in the metabolism, which are desirable in a study of the utilization of foods. On the other hand, the respiratory apparatus is advantageous because the exchange

of gases can be determined during short periods of fifteen minutes. It is disadvantageous, however, because, the periods being so short, errors at the beginning and end of the periods are magnified and because the individual must breathe through a nosepiece or mouthpiece, and this introduces an abnormal state. Unfortunately, in each form of apparatus, the error of a leak falls chiefly on the oxygen, because the patient and the apparatus constitute a closed circuit, and any diminution in gas in this circuit must be offset by the addition of oxygen. A more troublesome source of error and one difficult to avoid arises from the possibility of the patient exhaling carbon dioxide, which has previously accumulated in the body, at a more rapid rate than corresponds with the oxygen inhaled. The patient is said to "pump out" carbon dioxide. There is also another error due to carbon dioxide which is lost by cutaneous respiration, and it has been calculated that this would lower the quotient 0.01 to 0.15.

Many pitfalls, therefore, lurk in the determination of the respiratory exchange of an individual. The carbon dioxide is the more easily estimated of the two gases and in early experiments on metabolism investigators attempted this alone. The determination of oxygen is far more difficult. Hence, in dealing with the respiratory quotient, which depends on the relation of these two determinations to each other, one treads on very dangerous ground, and all statements regarding the respiratory quotient of individuals must be accepted with caution. The general picture of the respiratory quotient in an individual is far more valuable as a guide to his true metabolism if based on several experiments than is the result of a single experiment. Similarly, it is probably safer to average the results of a series of cases than to attach too much importance to figures obtained in one.

The Respiratory Quotient of the Normal Individual—The respiratory quotient of the normal individual is best determined at least twelve hours after a meal. It has been shown that if this rule is not followed the composition of the meal will have a marked influence on the result. Under these circumstances the respiratory quotient of normal individuals does not greatly vary. Benedict, Emmes, Roth and Smith²⁵ working at the Nutrition Laboratory of the Carnegie Institution, have studied the basal gaseous metabolism for 89 men and 68 women and their average results are shown in Table 8.

I would call attention to the slight difference existing between the respiratory quotient of men and women—0.83 and 0.81. I have also incorporated the heat production, calculated from the oxygen intake, which was approximately 25 calories per kilogram per twenty-four hours. This latter figure is lower than we are apt to consider, but it

25 Benedict, Emmes, Roth and Smith. Jour Biol Chem, 1914, 18, 139

should be remembered that it is based on fasting periods when the patient is purposely endeavoring to be quiet. It would be absolutely wrong, from such determinations covering periods of fifteen minutes, or even a few hours, to draw conclusions on the total heat production for the day. In illustration of the method and at the same time of the difficulties of determining the respiratory quotient of normal individuals I give the figures in my own case (Table 9)

TABLE 8—RESPIRATORY QUOTIENT AND TOTAL METABOLISM OF NORMAL INDIVIDUALS AT REST AT LEAST TWELVE HOURS AFTER THE LAST MEAL

Individuals	R Q	Calories per Kilo per 24 Hours
89 men 68 women	Average = 0.83 Average = 0.81	25.5 24.9

TABLE 9—RESPIRATORY QUOTIENT OF A NORMAL PERSON

Normal individual (E. P. J.) fasting experiment December 23, 1914. Weight, 64.9 kilos. Height, 177.8 centimeters.

Duration		CO ₂ Per Min c c	O ₂ Per Min c c	R Q	Calories per kilo per 24 hours
Min	Sec				
15	6	152	192	0.80	20.40
14	59	150	194	0.77	20.51
15	0	153	196	0.78	20.77

Average = 0.78

Naturally I took the greatest possible pains to be quiet and breathe in a normal manner, but it will be seen that whereas the values for the carbon dioxide of themselves, and of oxygen for themselves vary to an extremely small degree from period to period, yet they differ sufficiently to make a considerable variation in the respiratory quotient. This experiment emphasizes the possibilities for error in the determination of the respiratory quotient even under most favorable circumstances.

The respiratory quotient of individuals fasting for long periods is well exemplified by the studies made by Benedict¹⁵ on a man who went thirty-one days without food. These are illustrated in Tables 10 and 11.

It will be seen that, prior to the experiment, the respiratory quotient differed little from that of the group of normal individuals above mentioned. With the withdrawal of all food the respiratory quotient fell, and after the fifth day reached a point which Magnus-Levy²⁶ has said

26 Magnus-Levy. Ztschr. f. klin. Med., 1905, lvi, 83.

theoretically represents the quotient which is obtained when the metabolism consists of 85 per cent of fat and 15 per cent of protein, namely, 0.72. In other words, five days of starvation removed the last discernible influence of carbohydrate remaining stored in the body, and the individual lived wholly on body fat and body protein. It is possible to discover how much fat and how much carbohydrate take part in the metabolism.

TABLE 10—THE RESPIRATORY QUOTIENT OF A MAN DURING A PROLONGED FAST

Period	Time	R Q	Calories per Kilogram Body Weight
Preliminary Period	Fourth day before fast	0.81	33
	Third day before fast	0.89	32
	Second day before fast	0.89	29
	First day before fast	0.82	27
Period of Fast	Days 1—5 of fast	0.77 (Avge)	26
	Days 6—31 of fast	0.72 (Avge)	23
	Days 6—31, early a m	0.73 (Avge)	23
After Period	Second day after breaking fast*	0.78	25
	Third day after breaking fast*	0.94	27

* Twelve hours after food

TABLE 11—QUANTITIES OF PROTEIN, CARBOHYDRATE AND FAT OXIDIZED BY FASTING MAN AT NUTRITION LABORATORY²⁷

Period of Fast	R Q		Quantities Oxidized			Calories per kilo per 24 hours
	Actual	Non Prot	Protein gm	Carb gm	Fat gm	
1st Day	0.78	0.76	43	69	135	30
2d Day	0.75	0.74	50	42	142	30
3d Day	0.74	0.74	68	39	130	29
4th Day	0.75	0.71	71	4	136	28
5th Day	0.76	0.72	63	15	133	28
6th to 31st Day Average	0.72	0.70	53	0†	114	26

* Determined from the Daily Metabolism, the Urinary Nitrogen and the Calculated Non Protein R Q

† Actually a total of 32 gm carb were burned during the sixth to thirteenth day, inclusive, and later none

Knowing the nitrogen in the urine, one can calculate the amount of oxygen employed by the body for the oxidation of the protein²⁷ which it represents, and correspondingly, the amount of carbon dioxide given off can be determined. If we subtract these computed figures from the total carbon dioxide and oxygen obtained by direct experiment, we have left the carbon dioxide produced by the non-protein metabolism in the body, and the relation of the two gives the non-protein respira-

²⁷ In estimating the quantity of body protein burned from nitrogen in the urine the equivalent 6.00 is employed instead of 6.25

tory quotient In a useful table constructed by Lusk,²⁸ the percentage of carbohydrate and of fat for any given non-protein respiratory quotient between 70 and 100 can be calculated On this basis it was shown that Benedict's fasting man burned either no carbohydrate or only a trace after the sixth day When the respiratory quotient of this man was 0.73 on the seventh day it represented a nonprotein respiratory quotient of 0.70 and no carbohydrate was burned A respiratory quotient of 0.74 gave a nonprotein respiratory quotient of 0.71, which represents the oxidation of 3.8 gm of carbohydrate, a respiratory quotient of 0.76 gave a nonprotein respiratory quotient of 0.72, which is evidence that 15 gm carbohydrate were burned

Respiratory Quotient in Normal Individuals after Food—The respiratory quotient following the ingestion of food is shown well by the fasting man at the Nutrition Laboratory for the periods before fasting commenced It will be seen that twelve hours after food it varied from 0.81 to 0.89 in the four days Similarly, following the termination of the fast, the respiratory quotient rose, indicating the combustion of large quantities of carbohydrate

An experiment was performed on myself which was comparable to those later carried on with the diabetic patients when tests were made of the influence of food on their metabolism The changes in my own respiratory quotient following the ingestion of 60 gm of carbohydrate in the form of oatmeal are given in Table 12

It will be seen that the respiratory quotient within an hour rose some eight points after eating 60 gm of carbohydrate in the form of oatmeal It has been calculated that if 48 gm carbohydrate are burned in twenty-four hours at the rate of 2 gm of carbohydrate each hour continuously for the twenty-four hours, the respiratory quotient would rise 3 points—in other words, would be about 0.75 instead of 0.72, which is a fat-protein quotient I wish to emphasize the change in respiratory quotient of only 3 points when approximately 48 gm carbohydrate are burned at the rate of 2 gm carbohydrate per hour per day, and the rise of 8 points following directly on the ingestion of 60 gm carbohydrate The continuous combustion of small portions of carbohydrate amounts to the combustion of a considerable quantity of carbohydrate during the whole day, and yet it will raise the respiratory quotient very little The combustion of 24 gm of carbohydrate at the rate of 1 gm per hour could scarcely be detected with our present methods, and yet a tolerance for 24 gm carbohydrate is relatively a high tolerance when one is dealing with serious cases of diabetes

The Respiratory Quotient in Diabetes—In mild cases of diabetes, when the urine is free from sugar and the carbohydrate in the diet

28 Williams, Riche and Lusk Jour Biol Chem, 1912, xii, 357

large, the respiratory quotient differs little from that of normal individuals. The respiratory quotient of these same mild cases of diabetes will be lowered by fasting or by the withdrawal of carbohydrate, as just shown in the case of the normal fasting man. Undoubtedly the limited quantity of carbohydrate in the diet in cases of severe diabetes is responsible to a large degree for the low respiratory quotient which such patients show. Magnus-Levy called attention to this, and so

TABLE 12—METABOLISM OF A NORMAL INDIVIDUAL AFTER FOOD
Weight, 64.9 kilos Height, 177.8 cm

Date	Condition	CO ₂ Per Min cc	O ₂ Per Min cc	R Q	Calories Per Kilo Per 24 Hours
9/9/14	12 hours after breakfast	205	241	0.85	26
9/10/14	12 hours after breakfast	192	237	0.81	25
9/30/14	9 a m, fasting	159	194	0.82	21
	10.30 a m, after 60 gm carb as oatmeal	189	212	0.90	23
12/23/14	8 a m, fasting	152	194	0.78	21
	1 p m, fasting	151	196	0.77	21

TABLE 13—ILLUSTRATION OF FALL IN RESPIRATORY QUOTIENT OF MILD DIABETIC*
Case 714 Female Aged 38 years, 9 months Weight 53 kilos

Date	R Q	Urine Sugar	Diet †			
			Carb gm	Prot gm	Fat gm	Alcohol gm
Dec 3		4.4%	++	++	++	0
Dec 4 5		20 gm ‡	+	+	+	10
Dec 5 6	0.78	0	0	0	0	25
Dec 6 7	0.75	0	15	40	45	10
Dec 7 8	0.75	0	15	45	60	7
Dec 10 11	0.73	0	15	55	100	9

* Tests were made fasting at 8 a m, which was one hour after the collection of the twenty-four hour urine

† Approximate

‡ In fourteen hours

have other observers. It is well exemplified by the change in the respiratory quotient in Case 714. This patient, with only moderate acidosis, became sugar-free on April 16, 1914, following fourteen days of treatment. On Dec 3, 1914, she reentered the hospital with 4.4 per cent of sugar, but under fasting treatment became sugar-free after the omission of four meals. The respiratory quotient on successive days is shown in Table 13.

It will be seen that whereas the respiratory quotient was 0.78 on entrance, owing undoubtedly to the oxidation of some of the carbo-

hydrate ingested, though much at the same time was being lost in the urine, this rapidly decreased to 0.73 under starvation followed by a low carbohydrate diet. Yet this could not be considered a severe case of diabetes. The quotient was low simply because the woman was living almost exclusively on a fat protein diet.

The problem of drawing inferences from the respiratory quotient in diabetes is complicated by the fact that much of even the little carbohydrate which is given to a diabetic patient is lost in the urine. The patient really approaches the condition of the fasting man in that he is living exclusively on fat and protein, although in this case not that of his own body. If all the carbohydrate ingested is lost in the urine, his respiratory quotient would be 0.72. But there are other complications. Occasionally cases of diabetes are seen in which the sugar in the urine exceeds that of the diet, and speculation at once arises as to the source of this excess of sugar. Magnus-Levy²⁰ has pointed out that if the sugar in the urine amounted to 60 gm and the protein in the diet to 100 gm, the additional quantity of oxygen which would be demanded to form this amount of sugar out of protein would lower the respiratory quotient to 0.70. The situation is still further complicated by the presence of unoxidized acid bodies in the urine, amounting frequently to 20 to 40 gm and occasionally to 60 gm calculated as beta-oxybutyric acid. The amount of oxygen consumed in the formation of these bodies—for beta-oxybutyric acid is far richer in oxygen than are protein and fat—would again lower the quotient, and it has been calculated by Magnus-Levy that the respiratory quotient of a diabetic patient presenting 60 gm of sugar in the urine for 100 gm of protein in the diet, and excreting 20 gm of beta-oxybutyric acid, would fall as low as 0.69. For convenience, these figures are summarized. The respiratory quotient of the fasting man at the Nutrition Laboratory was 0.72. The calculated respiratory quotient of a normal individual who is burning 15 per cent protein and 85 per cent fat is 0.72. The theoretical respiratory quotient of a diabetic individual excreting all the carbohydrate in the diet, and 60 gm of glucose for each 100 gm of protein in the diet, is 0.70. The theoretical respiratory quotient of the diabetic individual excreting 60 gm glucose for 100 gm protein and 20 gm beta-oxybutyric acid as well, is 0.69. These calculations presuppose that the sugar and beta-oxybutyric acid excreted were formed during the same twenty-four hours, but who knows whether this is the case? The theoretical nonprotein respiratory quotient of a case of diabetes living on fat and the non-carbohydrate part of the protein molecule, as calculated by Lusk, is also 0.69.

Table 14 shows the theoretical respiratory quotient, which should be reached under varying conditions of diet for a normal individual,

and the changes which theoretically are present under special conditions in diabetes. Figures of this type have dominated the discussions of the metabolism in diabetes from the start, and whenever experiments have not produced figures comparable with these, they have often been considered erroneous. We are taught to believe that cases of diabetes are not severe unless the respiratory quotient is 0.69. It is questionable, however, whether the experimental data at our disposal enable us to say that our theories are backed up by the results which we obtain. If one looks over the lists of respiratory quotients obtained in successive periods with any variety of respiratory apparatus or calorimeter, he will be shocked at the discrepancy and forced to the belief that any argument based on a change in the respiratory quotient of one point is unjustifiable, and that any argument which is based on a change in the respiratory quotient of two points really hangs on a

TABLE 14—THEORETICAL RESPIRATORY QUOTIENTS (FROM MAGNUS-LEVY)

Diet	Calories	R Q
Protein, 100 gm ($100 \times 4.1 = 410$) Carb., 567 gm ($567 \times 4.1 = 2325$)	2,735	0.97
Protein, 100 gm ($100 \times 4.1 = 410$) Fat, 250 gm ($250 \times 9.3 = 2325$)	2,735	0.72
Loss in Urine Sugar, 60 gm ($60 \times 4.1 = 246$)	2,489	0.70
Loss in Urine Sugar, 60 gm ($60 \times 4.1 = 246$) B Oxy acid, 20 gm ($20 \times 4.7 = 94$)	2,395	0.69
Total loss = 340		

very slender thread. A change of three points is, however, deserving of consideration, but modesty should rule in conclusions which are to be drawn from any given set of experiments.

It is appropriate to discuss here what constitutes a severe diabetes. At the outset it can be said for our own encouragement that Naunyn did not pretend to be able to distinguish accurately between the various types. Usually by severe diabetes is understood those cases in which—to quote von Noorden—“notwithstanding a prolonged, extreme carbohydrate-free diet, the urine contains sugar.” By an extreme carbohydrate-free diet von Noorden undoubtedly meant one containing protein, fat and a few green vegetables—in other words, a diet with 10 gm carbohydrate, more or less—not a strictly fat-protein diet. The definition is also open to objection, because one frequently meets with cases of diabetes of long duration in which but a small per cent of the carbohydrate intake is excreted in the urine, yet this persists for many days on an extreme carbohydrate-free diet, but the case could not be classed as severe.

Another method of classification is adopted by Lusk, who considers cases severe in which, when the patients are put on a protein-fat diet, there is a dextrose-nitrogen ratio of 3.65:1. By this he means that 3.65 gm of dextrose appear in the urine for 1 gm of nitrogen, or the 6 gm of protein which it represents. In other words, 60 per cent (actually $3.65 \div 6.25 = 58.4$ per cent) of the protein burned by the body appears in the urine in the form of sugar. Lusk considers that this is the greatest possible amount of sugar which can appear in the urine on a carbohydrate-free diet, and he assumes that it comes wholly from protein. This conclusion has been reached with many observations on dogs, following injections of phloridzin, and by one case of diabetes coming under his personal observation, and he refers to other cases selected from the literature.

Unfortunately, or perhaps fortunately, neither of these methods of classification at the present time are wholly satisfactory, because, thanks to Dr Allen, our patients now become sugar-free very readily. It is possible that fasting will not remove the sugar from the urine of all diabetic patients, but this has been my experience with every case when I have followed Dr Allen's directions, and my experience coincides with that of many others. It may be that recent cases of diabetes have been of a different type from those hitherto encountered, but this is hardly possible. Consequently we cannot adopt the definition of von Noorden, and it is embarrassing to adopt the precise definition of Lusk. The dextrose-nitrogen ratio vanishes with fasting, and the clinician does not wish to expose his patient before beginning fasting to the dangers of a protein-fat diet simply to determine the severity of his case. I am hoping that with the added knowledge of diabetes which the introduction of fasting has brought about, Professor Lusk will pursue his studies further and give us definite rules for testing the severity of the disease. Perhaps definite quantities of protein alone or some special form of protein or derivative of protein could be administered to these patients, and the amount of sugar in the urine determined. Should this method not furnish satisfactory results, another series could be carried out in which varying quantities of fat as well as protein could be added, and if a third factor were necessary, the calories per kilo could be standardized. But we can trust Professor Lusk to give us help. Of course dextrose-nitrogen ratios are of little significance without simultaneous reports of the blood sugar.

In the data which will follow, consideration will be taken of both von Noorden's and Lusk's classification, but also the severity of the cases will be indicated by a statement of the time intervening between the period of observation and death in coma. It would seem as if the severity of the type of diabetes which resulted in death by coma should challenge criticism.

As the periods of observation before death in coma are of importance, the intervals between the determination of the respiratory quotient of the patient and death are given. See Table 16, which will later be discussed more in detail. This appears far more rational than to give the duration of the course of the disease, for many patients present a mild type of diabetes for many years, changing over to a severe type at a comparatively short period before death.

Table 15 summarizes the respiratory quotients of cases of diabetes considered severe by their observers.

TABLE 15—RESPIRATORY QUOTIENT IN SEVERE DIABETES

Year	Observers	Cases	R Q
1894	Weintraud and Laves <i>Ztschr f physiol Chem</i> , 1894, xix, 603	1	0.70
1897	Nehring-Schmoll <i>Ztschr f klin Med</i> , 1897, xiii, 59	2	0.72
1905	Magnus-Levy <i>Ztschr f klin Med</i> , 1905, lvi, 86	2	0.71
1907	Mohr <i>Ztschr f exper Path u Therap</i> , 1907, iv, 910	1	0.72
1908-1911	Benedict and Joslin <i>Carnegie Inst. of Washington, Publications</i> 136 and 176, 1910, 1912	19	0.73
1912	Rolly <i>Deutsch Arch f klin Med</i> , 1912, cv, 494	8	0.74
1912	Grafe and Wolf <i>Deutsch Arch f klin Med</i> , 1912, cvii, 201	3	0.74
1912-1914	Benedict and Joslin, 1914-15	7	0.73
		Total 43	Average 0.73

It will be seen that there is surprising unanimity of agreement among the different groups. It should be stated that Leimdorfer²⁹ has obtained much lower quotients varying between 0.64 and 0.68 with five cases which he considered severe. His figures, however, have not been generally accepted. One of the cases which he considered mild at no time showed a respiratory quotient above 0.70. According to the computations given above from Magnus-Levy, it was shown that, theoretically, in a diabetic patient with 60 gm of sugar in the urine for each 100 gm of protein in the diet—in other words, approximately the Lusk dextrose-nitrogen ratio—and with 20 gm of beta-oxybutyric acid, the respiratory quotient would not go below 0.69, and he further points out that, in order for the ratio to sink to 0.653, 150 gm of sugar must be formed from 150 gm of protein, and 40 gm of beta-oxybutyric acid must appear in the urine when the patient is on a diet of 150 gm protein and 250 gm fat. A respiratory quotient of 0.653 is a figure so low that it should be entertained with scepticism. The average respiratory quotient of 0.73 for forty-three cases of diabetes clinically considered severe is a far safer figure to follow than

29 Leimdorfer *Bio-Chem Ztschr*, 1912, xl, 326

to pick out one, two or three from the forty-three cases and say that these represent severe cases of diabetes and the others do not. The errors of the determinations of the quotients are so great that the average figures are safer than the individual ones. These respiratory quotients, as Grafe and Wolf³⁰ pointed out, show that at least some carbohydrates were being oxidized by severe diabetic patients. They also pointed out that with the improvement of patients the respiratory quotients increased from 0.743 to 0.817 in a fasting condition.

These figures suggest at the first glance that very little carbohydrate was burned in this group of severe cases of diabetes. The respiratory quotients are identical with the quotients obtained under similar conditions with the fasting man at the Nutrition Laboratory, though his average for the whole day for the fasting period was 0.72. But we must remember that two corrections are to be made in these figures, first, sugar has been lost in the urine which has been formed from protein, and second, there have been varying amounts of beta-oxybutyric acid, diacetic acid and acetone excreted. Both of these processes represent processes of oxidation and by demanding additional oxygen for which no carbon dioxide is produced tend to lower the respiratory quotient. Therefore, if we grant that the series represents cases of severe diabetes, we must reach the conclusion that these diabetic patients utilized some carbohydrate, and that their respiratory quotients would have been several points above 0.73, had they not been lowered to 0.73 by the production of sugar from protein and the formation of acid bodies.

Are the cases reported in Table 15 severe? At least no cases of greater severity have been hitherto published. By von Noorden's criterion they might be considered severe, for they did not become sugar-free with restricted diet, yet it is true that this restricted diet was not so rigid as is often employed on account of the marked acidosis. If we accept Lusk's criterion (and I am not ready to do so until a second human case is studied under modern conditions³¹) they were not severe. Not one of Benedict's and my cases showed a persistent D/N ratio of 3.65/1. Yet the clinical facts point to severity. In the first group of nineteen cases of diabetes reported in 1908-1912 by Benedict and myself, eighteen patients are dead and of these fifteen

30 Grafe and Wolf. *Deutsch Arch f klin Med*, 1912, cvii, 201.

31 By modern conditions I mean (1) exclusive fat-protein diet, (2) under surroundings which make errors in diet impossible, (3) a duration of at least seven days to exclude the washing out of stored carbohydrate, (4) a constant (not falling) D/N ratio of 3.65/1 for the last three of the seven days, and (5) several daily blood sugar determinations to furnish some proof, inadequate though it be, that the sugar in the urine has not come from that left over in the blood. At present I cannot advocate such a test because of the danger of acidosis, and believe it better to leave the question in this form, undecided.

died in coma. This fact can be taken as a measure of their severity. I do not believe, however, that this alone justified us in saying that a case of diabetes is of the severest type. I conceive it possible, for a moderately severe case of diabetes, by sudden changes of diet, to be driven into coma accidentally. This was done years ago, when diabetic patients who were living on a free diet on coming to the hospital were suddenly deprived of carbohydrate and the fat and protein were increased. It appears to me quite probable that most cases of coma in diabetes have occurred long before the disease had reached its greatest severity, and I wish to point out that therein lies great hope for the future.

It will be of interest, however, to note the respiratory quotient of a group of six cases of diabetes all ending in coma, death occurring within a period of 44 to 14 days from the time of observation, and to compare these with a group of patients whose respiratory quotient was observed at a greater interval from death by coma. This is shown by Table 16.

TABLE 16—RESPIRATORY QUOTIENT IN SEVERE DIABETES. COMPARISON OF FATAL CASES AND CASES OF LIVING PATIENTS

Fatal Cases			Living Patients		
No. of Cases	Days Before Coma	R Q	Case No.	Days Before* March 1, '15	R Q
6	44-14	0.71	552	801	0.72
8	442-70	0.74	765	125	0.73
			786	111	0.71
			806	72	0.70
			4 Cases	801-72	0.715

* All of these patients were in good condition May 1, 1915, which would add sixty-two days to the duration since the observations were made.

A consideration of this table suggests that with approaching death the respiratory quotient falls. It will be seen that the cases ending fatally within a period of from 44 to 14 days from the time of observation, gave a quotient of 0.71, as contrasted with a quotient of 0.74 in cases terminating fatally in coma at an interval from death of from 442 to 70 days. If we had these figures alone, the inference might be justified, but caution is necessary before drawing such a conclusion. Four living diabetic patients show a respiratory quotient almost as low—0.715. Instead of progression toward death by coma, their general condition has improved. In other words, a falling respiratory quotient does not necessarily mean approaching death by coma. It does mean that these patients have lived for prolonged periods on an almost exclusively fat-protein diet and suggests that they are forming carbohydrate out of protein and producing acid bodies.

It should be said that all of these living patients have been treated either by much restricted diets or by fasting as advocated by Dr Allen. When they were first seen the cases appeared to be quite as severe as those earlier studied which ended fatally in coma. What shall we say of them at present? None of these patients can be considered well, but all lead a comfortable life at home.

The group of patients dying within a period of from forty-four to fourteen days deserves further comment. The average quotient of these cases was 0.71. From four of these the non-protein respiratory quotient has been reckoned, and it amounted to 0.695. This respiratory quotient implies that much material must have been formed in the course of the metabolism which used a portion of the oxygen. This was especially true of Case 246, in which there was a respiratory quotient of 0.69, which was based on an average of twenty-nine periods, most of which were fasting.³² Stimulated by inquiries from Professor Lusk, I am fortunately able to show the cause of the particularly low quotient in this patient. His diet and urinary analyses will be found in Tables 17 and 18. The average daily urinary nitrogen for the six days of observation was 16.6 gm., and it was considered that this represented approximately the metabolism of 100 gm. protein. The beta-oxybutyric acid was 46.6 gm. daily and allowing for acetone and diacetic acid the total excretion of acid bodies was assumed to be 60 gm. The fat in the diet as originally recorded was probably inaccurate, and I believe 165 gm. daily near to the exact quantity. From these tables it will be seen that the daily carbohydrate in the diet was 71 gm., and the dextrose excreted was 102 gm. giving a minus balance of 31 gm. This, with the 16.6 gm. nitrogen in the urine, gives a D/N ratio of only 1.9 to 1. In Table 18 are placed the data from which the respiratory quotient can be calculated from the diet and urine, and they show that after deductions for dextrose and acetone bodies, the theoretical quotient would be 0.692, which it will be remembered was identical with the respiratory quotient found by experiment. These tables are submitted as proof that a quotient of 0.69 does not necessarily mean that the capacity for burning carbohydrate has been totally abolished.

Computations of a similar character by Grafe and Wolf³⁰ lead to the same conclusion.

According to these writers, "the conception which on the whole appears to have the greatest probability is that even the severest diabetic has at his disposal 20 to 30 gm. of glycogen for combustion or synthesis, thirteen to twenty hours after a meal containing a minimal

³² Benedict and Joslin. *Metabolism in Diabetes*, Pub. Carnegie Institution of Washington, 1910, No. 136, p. 68.

amount of carbohydrate Perhaps the complete loss of the power of combustion of sugar is, broadly speaking, no longer consistent with life "

TABLE 17—METABOLISM IN A CASE OF SEVERE DIABETES WITH A RESPIRATORY QUOTIENT OF 0.69 *

Case C, No 246 Male Acute onset at 28 Death in coma in fifteen months

Day	Urine					Diet				Sodium Bicarb Gm
	Volume, cc	N, Gm	NH ₃ Gm	B oxy, Gm	Dex-trose, Gm	Carb, Gm	Prot, Gm	Fat, Gm	Alco hol, Gm	
1	2,935	16.3	4.8	29	72	15	18	55	15	0
2	3,710	18.3	5.0	34	106	98	22	225	30	0
3	4,370	19.6	5.5	61	134	65	100	200	30	60
4	4,035	19.4	5.4	61	107	65	100	200	30	60
5	3,380	14.7	5.6	46	100	125	45	100	30	25
6	3,765	16.3	5.0	48	93	65	100	200	22	25
Ave	3,691	16.6	5.2	46.6	102	71	65	165	26	28

*Daily protein metabolism estimated at 100 gm Total acetone bodies estimated at 60 gm
Carbohydrate in diet, 71 gm
Dextrose in urine, 102 gm
Carbohydrate balance, 31 gm
D N ratio, 1.9 : 1.0

TABLE 18—To SUPPLEMENT TABLE 17 *

Case C, No 246

Diet	Gm	Calories	O ₂ Liters	CO ₂ Liters	R Q
Protein	100 × 4.1 =	410	96.6	78.2	0.756
Fat	165 × 9.3 =	1535	333.1	235.5	
Carbohydrate	71 × 4.1 =	291	58.9	58.9	
Alcohol	26 × 7 =	182	37.9	25.3	
		2418	526.5	397.9	
Lost in Urine					
Dextrose	102 × 3.7 =	337	76.1	76.1	0.692
Acetone bodies as B oxyb	60 × 4.5 =	243	58.1	51.6	
		620	134.2	127.7	
		1798	392.3	270.2	

* The respiratory quotient found, based on an average of 29 periods, chiefly fasting was 0.69

Effect of Food on Utilization of Carbohydrates in Severe Diabetes
—A moderate number of experiments on the effect of food on severe diabetics has been recorded, but the actual number of experiments to determine the effect of carbohydrate on the respiratory metabolism is very limited Such experiments have been published by Leo,³³ who

33 Leo Ztschr f Klin Med, 1891, xix, 101

considered that the respiratory quotient did increase in two cases of severe diabetes, although this was not uniformly the rule and he concludes that even in severe diabetes a part of the sugar ingested or formed in the body is utilized

Nehring and Schmoll³⁴ tested the effect of carbohydrates also in two severe cases of diabetes, but were unable in either to show an increase in the respiratory quotient. Frequently a fall instead of a rise in the quotient took place. Benedict and Joslin,³⁵ in a series of experiments chiefly with bread and dextrose, state that "the ingestion of carbohydrate produced no very material alteration in the metabolism as a whole," and later "no evidence can be found of a combustion of carbohydrate." Two years later a series of experiments with oatmeal and levulose were reported, but without comment.³⁶

Rolly,³⁷ in a series of experiments, tested the comparative effects of oats, rye, wheat, lentils and green cornmeal on diabetic patients. Unfortunately, few of the experiments were preceded by control periods. Two of his cases he considers severe. In Case 1, at three, five and six hours after 70 gm of oatmeal were administered, the respiratory quotient was 0.73. After 70 gm of wheat meal it was 0.76. The respiratory quotient of his Case V after 80 gm of oatmeal was 0.71, after 80 gm of rye meal was 0.73, and after 80 gm of wheat meal was 0.71. Two of his other cases were only moderately severe, and the other only a light case, and all showed an increase in the respiratory quotient after their meals reaching up to 0.83, 0.85 and 0.84 respectively. It will be noted, furthermore, that of the two severe cases, in the first the quotient following administration of wheat meal which was given after oatmeal reached 0.76.

Roth³⁸ records slight increase of the respiratory quotient following the administration of carbohydrate. The experiments, however, lose much of their value because of the absence of fasting controls on the day the carbohydrates were given.

Falta¹⁹ has mentioned several experiments designed to show the effect of the oatmeal cure on the respiratory quotient. The data of the experiments are not given, but he states that with one moderately severe diabetic the respiratory quotient rose only on the third day of an oatmeal cure, in which 400 gm had been given daily. Despite this

34 Nehring and Schmoll. *Ztschr f klin Med*, 1897, xxxi, 59.

35 Benedict and Joslin. *Loc cit* (Note 32) p 215.

36 Schilling. *Inaug Dissert*, Leipzig, 1911, tested the effects of various meals on the respiratory quotient of one severe, one mild and two moderately severe cases of diabetes, and demonstrated no specificity for oatmeal. With the severe case the results were inconstant, but usually tended to show a slight increase in the respiratory quotient.

37 Rolly. *Deutsch Arch f klin Med*, 1912, cv, 494.

38 Roth. *Wien klin Wchnschr*, 1912, xlvii, 1864.

enormous quantity of oatmeal, no glycosuria was observed. It is unfortunate that I have not been able to find a later publication which was promised. He furthermore makes the interesting statement, which is so remarkable as to invite confirmation, that a similar result was encountered with a normal individual, whose carbohydrate depots had been robbed by living on a diet poor in carbohydrates for a long time. It would appear that only after these depleted stores were replenished, did the normal individual, begin to burn carbohydrate. His results are in striking contrast to the changes in respiratory quotient which were shown by the fasting man at the Nutrition Laboratory. At the end of his fast of thirty-one days he ate food almost exclusively in the form of carbohydrate and the quotient promptly rose to 0.79 and 0.96 on the second and third days respectively, emphasizing the fact that in a mixed diet carbohydrates are burned much earlier. He further states that on a meat diet or on a diet with a moderate amount of carbohydrate the diabetic patient seldom shows a quotient above 0.74, and he also noted the fact, to which attention has been called by Nehring and Schmoll, and which is also borne out by our own series of cases, that following the administration of carbohydrate a considerable quantity of carbohydrate not only remains in the body, but the respiratory quotient remains low. Intravenous injections of sugar (30 gm.) given by Falta to severe diabetics, who had eaten 300 gm. of oatmeal for three days without glycosuria, brought about an evident glycosuria, but the respiratory quotient rose proportionately little. In the case of a severe diabetic there was no increase, but a still further lowering of the already low respiratory quotient.

The present series of experiments with foods which I have to report represent a part of the experiments on diabetics whose metabolism following the administration of food was studied at the Nutrition Laboratory since 1910.

Three experiments have been conducted with levulose. In Case 332 100 gm. of levulose were administered when the patient was fasting. This patient was a severe diabetic, weight 40 kg., in the twenty-fourth month of her illness, and died five months later. The respiratory quotient before the levulose was administered was 0.72, and following the levulose the quotient was determined in six different periods during the following three hours and showed an average of 0.69. Despite the fall in the respiratory quotient, the total metabolism increased markedly, although apparently most of the levulose was excreted in the urine. Unfortunately, it is impossible to state how much of the 120 gm. of sugar in the urine for this twenty-four hours came from the levulose and how much from carbohydrates of the preceding day.

Our records indicate that the patient was on a diet containing approximately 100 gm of carbohydrate. This fact is of interest in comparison with the next two cases, in which also levulose was given.

TABLE 19—EFFECT OF LEVULOSE ON A SEVERE DIABETIC

Case 332 Female Aged 37 years Weight 40 kilos

Time	Condition	CO ₂ Per Min	O ₂ Per Min	R Q	Calories per Kilo per 24 Hours
3/31/11	Fasting	cc	cc		
10 50	Fasting	151	205	0.74	35
11 23	Fasting	145	211	0.69	36
100 gm levulose					
12 16		172	271	0.63	46
12 44		184	261	0.70	44
1 30		180	246	0.73	42
2 05		172	235	0.73	40
2 28		171	250	0.68	42
2 53		166	240	0.69	40
4/2/11					
8 17	Fasting	148	199	0.75	34
8 45	Fasting	151	203	0.74	35
9 14	Fasting	154	213	0.72	36
Oatmeal = 70 ± gm carb, 38 gm butter					
10 13		163	234	0.70	39
10 39		167	228	0.73	39
11 08		177	238	0.75	40
12 12		170	230	0.74	39
1 28		154	206	0.75	35
2 37		163	209	0.78	36

TABLE 20—EFFECT OF LEVULOSE ON RESPIRATORY QUOTIENT OF DIABETIC PATIENTS

Case	Duration, Months	Month Observed	Carbo- hyd Preceding Day, Gm	Levu- lose, Gm	Sugar in Urine 24 Hours, Gm	R Q	
						Before	After
332	Dead 28	23	100±	100	120	0.72	0.69
552	Alive 32	18	30	100	3	0.72	0.76
785	23	20	20	81*	7	No Increase	

*81 gm levulose and later
9 gm carb as vegetables

90 gm total

In Case 552 also 100 gm of levulose was administered, but this was given after a prolonged period of low carbohydrate feeding. On the day previous to the experiment the carbohydrates in the diet amounted to 30 gm. The quantity of sugar in the urine in this case during the twenty-four hours of the experiment was 3 gm. The

respiratory quotient rose 4 points, namely, from 0.72 to 0.76 after the levulose

The third case, No 785 (Table 20), was that of a boy, aged 16, with severe diabetes of twenty months' duration, weight 42 kg. He had been made sugar-free by prolonged fasting and had been kept on a diet low in carbohydrate and protein, as well as fat. During the twenty-four hours of the test, the urine contained but 7 gm of sugar. Notwithstanding this fact, the respiratory quotient showed no increase, but a fall of 2 points. The actual figures are not published now, but the comparative values may be considered trustworthy. The evidence in these three cases, therefore, points to no utilization of the levulose in two of the cases. In one of these most of the levulose was probably excreted, but in the other only a negligible quantity. In the third case

TABLE 21—EFFECT OF POTATO ON RESPIRATORY QUOTIENT IN SEVERE DIABETES

Case Number	Duration Months	Month Observed	Carbohydrate Intake		Sugar in Urine 24 Hours, Gm	R Q	
			Preceding Day, Gm	Test Day, Gm		Before	After
765	7	3	15	63* 22 85	29	0.74	0.73
806	6	3	10	60† 6 66	3	0.68	0.71

* 48 gm carb as potato }
 10 gm carb as oatmeal } 63 gm Later in day, 22 gm carb as potato and vegetables
 5 gm carb as cream }
 Also 1 egg and 30 gm butter
 † 60 gm carb as potato Later in day, 1 egg, butter, 6 gm carb as vegetables

there was an increase of three points in the respiratory quotient, indicating a slight utilization of the levulose and there was no excretion of levulose of account.

It was possible to determine the effect of the administration of potato in two cases. In the first case the experiment was complicated in that the patient was given a small quantity of oatmeal at the start, which, however, was stopped on account of her dislike to it, and potato was substituted. In this case, No 765, no change in the respiratory quotient took place, but in the second, Case 806, a slight increase was noted, and apparently rather more than would be accounted for by the limits of error.

Eleven experiments have been carried out on cases of severe diabetes with oatmeal. These were arranged in some cases to determine the immediate effect of the administration of oatmeal, and in other cases to determine the effect of the prolonged administration of

TABLE 22—EFFECT OF POTATO ON THE RESPIRATORY QUOTIENT OF A SEVERE CASE OF DIABETES

Case 806 Male Weight 62 kilos

Date 12/22/14	Condition	CO ₂ per Min, c c	O ₂ per Min, c c	R Q	Cals per kilo per 24 Hrs	Blood Sugar Per Cent
9 25	Fasting	156	223	0 70	24	
9 54		150	224	0 67 0 68	24 21	
10 22		155	228	0 68	25	
10 45	Potato = 60 gm carb					0 14
10 55						0 18
11 59		181	257	0 71	28	
12 22		168	252	0 67 0 69	27 27	
12 55		172	250	0 69	27	
3 00		170	233	0 73	26	
3 26		157	227	0 70 0 72	25 25	
3 54		166	231	0 72	25	
4 45						0 19

TABLE 23—EFFECT OF OATMEAL ON THE RESPIRATORY QUOTIENT OF A SEVERE DIABETIC

Case 773 Female Weight 40 kilos

Date	Condition	CO ₂ per Min, c c	O ₂ per Min, c c	R Q	Cals per kilo per 24 Hrs	Blood Sugar Per Cent
10/10/14 8 00	Fasting	146	212	0 69	36	
	Oatmeal = 42 gm carb					
11 00		178	249	0 72	48	
10/13/14 8 00	Fasting	138	189	0 73	33	0 32
11 00						0 27
10/19/14 9 00	Fasting	135	195	0 70	34	0 27
	Oatmeal = 80 gm carb					
12 00		167	237	0 70	40	0 30
10/20/14	After breakfast					0 34

Diet contained 15 gm carb October 9 and October 18

TABLE 24—EFFECT OF OATMEAL ON THE RESPIRATORY QUOTIENT OF SEVERE DIABETICS

Case No	Duration		Date	Carbohydrates Ignited		Respiratory Quotient		Sugar in Urine, Gm	Carb Intake, Gm	Carb Balance, Gm
	Onset to Coma, Months	Month of Test		Day Preceding, Gm	Before Test Gm	Fasting	After Oat meal			
194	34	31	9/22	15		0.74		42	15	-27
			9/23	15	100+	0.71	0.71	50	165	+115
			9/24	165		0.72*		19	15	-4
246	15	11	8/ 9	50	40	0.71	0.67	124	?	?
		13	10/29	65	60	0.68	0.70	100	125	+25
			10/30	125		0.71*		93	65	-28
			10/25 31	71		0.69		102	72	-30
281	19	17	12/ 1	15		0.75		69	135	+66
			12/ 2	135	29		0.76*	58	45	-13
			12/ 3	45	0	0.76		38	30	-8
332	28	13	5/19	100	25±		0.73	15		
			5/26	95		0.73		in 3 hrs 3		
		24	4/ 2	?	52	0.74	0.74	in 3 hrs 97		
		26	6/ 2	?	48	0.71	0.69	36		
336	132	127	5/18	20		0.73		26	45	+19
			5/21	45	25		0.75	51	45	+14
441	11	9	9/29	15	75	0.70	0.71	65	165	+100
		10	10/ 9	15	73		0.69	?	79	
561	33	23	2/ 7	60		0.75		31.1	60	+30
			2/ 8	60	116	0.71	0.74	128.4	185	+57
			2/ 9	185	200	0.72*	0.72*	209.3	205	-4
			2/10	200		0.76†		101.86	60	-42
591	50	44	4/10	?		0.74		63	30	-33
			4/11	30		0.73		37	15	-72
			4/12	15	80	0.70	0.70	85	165	+80
			4/13	165	80	0.73*	0.69*	77	165	+88
			4/15	40		0.69		29	?	
773	20	18	10/ 8	115	70		0.70	175.6	165	-10
			10/10	15	47	0.69	0.72	95.4	130	+35
			10/13	50		0.73		83.97	50	-34
			10/19	15	80	0.70	0.70	96.50	115	+18
746	22‡	18	10/ 7	65	28		0.73	93.11	65	-28
			10/ 9	15	50	0.73	0.71	86.69	163	+76
			10/10	165		0.72*		34.88	25	-10
			10/15	165	80		0.74†	96.28	165	+69
786	17‡	14	11/12	15	60	0.69	0.73	0	62	+62

* R Q taken following an oatmeal day

† R Q taken subsequent to two oatmeal days

‡ Prior to March, 1915

oatmeal It will be seen from a study of the tables that as a rule the respiratory quotient remained stationary or fell; in one case it rose 4 points, and in two other cases it rose one point It will be noted further that the respiratory quotient, when taken fasting on the morning following an oatmeal day, amounted in three cases to 0.73, 0.72 and 0.73 respectively, and that on the morning following a second oatmeal day it was 0.69 and 0.76 The respiratory quotient was also determined in three experiments after the administration of carbohydrate and on the second day it was 0.72 If one looks at the table as a whole, it will be seen that little change in the respiratory quotient took place in fact, none of any account except on the morning following the second oatmeal day

The sum total of the results following the feeding of levulose, potato and oatmeal to severe diabetics affords little evidence, from the respiratory quotient, that the carbohydrate was burned, save in the case of one of the experiments with levulose, one with potato, and one with oatmeal There results correspond closely with what has been recorded in the literature Personally, I believe that before a final decision on this point can be reached from this particular line of study, further experiments must be performed

Unfortunately in the experiments recorded no stated agreement was noted between changes in respiratory quotient and variations in the quantity of blood sugar From Table 6 it is evident that there is a general tendency for the respiratory quotient to rise with an increase in blood sugar, but this may be accidental Studies now in progress will soon throw light on this phase of the question

V ACIDOSIS AS A MEASURE OF THE UTILIZATION OF CARBOHYDRATES

It has been generally accepted that acidosis will appear when carbohydrate food is either withdrawn from the diet or excreted in the urine It has been unquestionably the universal clinical experience that the patient who excretes quantities of sugar in the urine equal to or in excess of that in the diet exhibits acidosis, and that patients do not show acidosis who are able to utilize approximately 70 gm of carbohydrate, or large quantities of protein from which carbohydrate may be formed This statement cannot be so unqualifiedly made, because I have under observation a woman who in her sixth month of pregnancy showed over 6 per cent of sugar, and later under a careful diet became sugar-free, acquired a tolerance for approximately 100 gm of carbohydrate, and yet a slight acidosis persisted Nevertheless, the general mass of evidence points to the disappearance of acidosis when carbohydrates are burned, and on this general concept arguments have been based for and against the utilization of carbohydrate in severe diabetes

During von Noorden's oatmeal treatment a considerable quantity of carbohydrate ingested is usually retained or burned in the body, and the decrease of acidosis at the same time is usually considered evidence of the latter supposition being correct, but occasionally the acidosis persists although the carbohydrates are not excreted. I doubt if we are in a position to accurately explain the disappearance or non-disappearance of acidosis under these conditions. Oatmeal and other carbohydrates are better retained in the body following starvation, and it is quite possible that a mechanical retention of acid bodies goes hand in hand with the retention of carbohydrate. Magnus-Levy pointed out long ago that these were seldom excreted in concentration of more than 1.5 per cent, and that the fall in acidosis during an oatmeal cure may be simply apparent, because the volume of urine excreted has diminished. The influence of preceding fasting is also important, because this undoubtedly regulates to some extent the storage of carbohydrate. Despite these possibilities, which lessen any argument for combustion of carbohydrate based on the decrease of acidosis following the ingestion of carbohydrate, the slight amount of acidosis which is usually found when diabetic patients are on a full carbohydrate diet points strongly to the view that some carbohydrate is burned. The increase in respiratory quotient on the last days of an oatmeal cure, which Falta observed and we also have noted, is conformatory to this position.

Various writers have observed that the acidosis in diabetics decreases on a vegetable day or fasting day, but it remained for Allen to demonstrate conclusively the remarkable fact that acidosis vanished in practically all severe cases of diabetes under these conditions, and that in the remainder, if carbohydrates to a moderate extent are allowed temporarily the acidosis wholly clears up. If a normal individual fasts, it has been the universal experience of observers that acidosis appears. In other words, the normal fasting individual corresponds with the concept that when carbohydrates are withdrawn from the diet (and this implies carbohydrates which might be formed from protein) acidosis appears. Thus, in the fasting man at the Nutrition Laboratory, acidosis appeared on the second day and continued until the fast was terminated. How can we reconcile the apparent contradiction in the fact that fasting, which dissipates acidosis in diabetes, produces it in normal individuals? Must the prevalent conception be given up that carbohydrate oxidation and acidosis are unrelated and must we acknowledge that here is an instance where the absence of the burning of carbohydrates does not lead to acidosis? Such a conclusion appeared unavoidable until observations at the Nutrition Laboratory on severe diabetics during prolonged fasting began to accumu-

late, showing that whereas at the beginning of the fast the respiratory quotient was the ordinary respiratory quotient of severe diabetes, 0.72, with a continuance of the fast this had a tendency to rise several points, occasionally even to the neighborhood of 0.80. Later experiments, as yet unpublished, at the Russell Sage Laboratory made under the direction of Dr. DuBois and Professor Lusk on one of Dr. Allen's patients suggested a similar condition. In other words, whereas the normal individual showing acidosis exhibits a respiratory quotient based on the combustion of protein and fat alone, the severely affected diabetic during fasting shows a respiratory quotient which could be accounted for only by the combustion of notable quantities of material other than fat and protein. That this material was not protein was evident, because the amounts of nitrogen in the urine excreted during these periods were not abnormal. This increase in the respiratory quotient furnishes the explanation of the fact that the severely affected diabetic in contradistinction to the normal individual, shows no acidosis during a fast.

Several explanations for this increase in the respiratory quotient of fasting diabetics are available. During fasting the diabetic may be able to draw on sources of carbohydrate in the body which the normal individual cannot. Furthermore, the diabetic has in the body undoubtedly more carbohydrate stored than we have hitherto supposed, and the supposition must be entertained that the diabetic really may actually have more carbohydrate in some form in the body than exists in the normal individual. A third supposition for the increase in the respiratory quotient is that considerable quantities of acid bodies have accumulated and that with the improvement of the condition of the patient during fasting these are burned. It will be remembered that beta-oxybutyric acid, diacetic acid and acetone all have relatively high respiratory quotients, namely, 0.89, 1.00 and 0.75 respectively, and therefore the oxidation of a small quantity of these substances would markedly raise the respiratory quotient. Which of these suppositions is correct will be eventually known because of the improved methods of estimating carbohydrate and acid bodies in the blood, fluids and tissues of the body,³⁹ and also by the help which is afforded from the estimation of the carbon dioxide tension of the blood.

I should like to point out this further possibility. During prolonged fasting, acidosis tends to disappear, in part because the sources of the acid bodies, save for body fat and protein, have been eliminated. So soon as acidosis begins to decrease, there is, as we and others have found, a lessening of the total metabolism, and with this lessening of total metabolism an improvement in the combustion of carbohydrate

³⁹ Marriott Jour Am Med Assn, 1914, LXIII, 397

takes place. This in turn favors the combustion of acid bodies. It might well be that the first step to take in the treatment of a case of diabetes is to abolish acidosis completely.

All may be ready to concede that all diabetic patients under fasting conditions are burning carbohydrates, but some may say that the character of the disease has changed, and instead of being a severe type of diabetes the case has become one of moderate severity. Such a criticism is hard to answer. It presupposes, however, that an individual can readily change in the space of a few hours from a state in which death is imminent to one of safety, and that so fundamental a function as the loss of power to utilize carbohydrates can be quickly regained. This would be a remarkable phenomenon. Against this explanation also is the fact that many who have employed fasting treatment with severe cases of diabetes have regretfully acknowledged that either very slight or no increase of tolerance for carbohydrates has been produced in these patients. This would make it still more unlikely that the diabetic patient by fasting altered his nature. It would rather point to the view that the diabetic condition remained unchanged, but that during fasting the diabetic was able to secure and burn material which under other conditions he could not reach, and which the normal individual could not secure.

In conclusion it is gratifying to be able to record that the recent experimental evidence confirms the old clinical view that the severe diabetic still retains power to utilize a portion of the carbohydrate of his diet, small though it may be and that herein lies renewed hope for the success of treatment.

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RENAL FUNCTION AS MEASURED BY THE ELIMINATION OF FLUIDS, SALT AND NITROGEN, AND THE SPECIFIC GRAVITY OF THE URINE *

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During the last few years the study of renal function has largely confined itself to the determination of kidney activity as measured by the quantitative excretion of various dyestuffs and chemicals, either those normally found in the urine or foreign substances which have been fed or injected. By observing the kidney in this manner, notable results have been obtained, especially with phenolsulphonephthalein, lactose, potassium iodid, urea, salt and kreatinin. In most instances, the outcome of intensive study has been the discovery that the elimination of nearly all of these substances may at times be increased quantitatively, in spite of marked renal lesions or their complications, such as uremia. To supplement such tests, Hedinger and Schlayer¹ have recently proposed a qualitative test of the mode of urinary function, as measured by the specific gravity, salt and water excretion in two-hourly periods. These authors show how the urinary response to a full dietary containing a reasonable amount of fluids, salt and purins varies in health and disease. They found that the normal and the nephritic individual differ very markedly from one another in the results obtained with the so-called "nephritic test meal." Not only can the absence or presence of impairment of renal function be determined, but likewise its intensity.

The present paper records the results of studies carried out along lines suggested by this work. The test meal has been simplified somewhat, and it appears that the entire procedure, or a part of it, may very well become a valuable routine test for the general practitioner.

This test has now been carried out in more than one hundred cases. The only patients not investigated, in whom renal function should be ascertained, were those suffering from the acute nephritides, of these, such as have been treated in the wards of the hospital during the past winter have been too sick to take food in any quantity, or have been so unmanageable as to preclude the proper collection of specimens. It has been ascertained that the nephritic test meal, when duplicated on

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* From the Medical Clinic of the Johns Hopkins Hospital, Baltimore

1 Hedinger and Schlayer. *Deutsch Arch f klin med*, 1914, cxiv, 120

the same patient, yields identical results, provided the clinical condition has not changed. In several instances triplicate and quadruplicate observations have been made. Lack of space prevents the detailed report of all the findings.

The directions for the nephritic test meal are contained in the following memoranda, given to the nurse in charge of the case in mimeographed form.

NEPHRITIC TEST DIET

For

Date

All food is to be *salt free* food from the diet kitchen.

Salt for each meal will be furnished in weighed amounts*.

All food or fluid not taken must be weighed or measured after meals and charted in the spaces below.

Allow no food or fluid of any kind except at meal times.

Note any mishaps or irregularities that occur in giving the diet or collecting the specimens.

Breakfast, 8 a m

Boiled oatmeal, 100 gm

Sugar, 1-2 teaspoonfuls

Milk, 30 cc

Two slices bread (30 gm each)

Butter, 20 gm

Coffee, 160 cc

Sugar, 1 teaspoonful } 200 cc

Milk, 40 cc

Milk, 200 cc

Water, 200 cc

Dinner, 12 Noon

Meat soup, 180 cc

Beefsteak, 100 gm

Potato (baked, mashed or boiled), 130 gm

Green vegetables, as desired

Two slices bread (30 gm each)

Butter, 20 gm

Tea, 180 cc

Sugar, 1 teaspoonful } 200 cc

Milk, 20 cc

Water, 250 cc

Pudding (tapioca or rice), 110 gm

Supper, 5 p m

Two eggs, cooked in any style

Two slices bread (30 gm each)

Butter, 20 gm

Tea, 180 cc

Sugar, 1 teaspoonful } 200 cc

Milk, 20 cc

Fruit (stewed or fresh), 1 portion

Water, 300 cc

8 a m—No food or fluid is to be given during the night or until 8 o'clock the next morning (after voiding), when the regular diet is resumed.

Patient is to empty bladder at 8 a m and at the end of each period, as indicated below. The specimens are to be collected for the following periods in properly labeled bottles, to be furnished by the Chemical Division of the Medical Clinic.

* One capsule of salt, containing 23 gm of sodium chlorid, is furnished for each meal. The salt which is not consumed is returned to the laboratory, where it is weighed, and the actual amount of salt taken is calculated.

8 a m - 10 a m , 10 a m - 12 n , 12 n - 2 p m , 2 p m - 4 p m , 4 p m - 6 p m ,
6 p m - 8 p m , 8 p m - 8 a m

Specimens are to be left in ward until called for at 8 30 a m by attendant from the chemical laboratory

The above dietary contains approximately 13.4 gm of nitrogen, 85 gm of salt, 1,760 c c of fluid, and a considerable quantity of purin material in the meat, soup, tea and coffee. All these substances act as diuretics, and it is on the mode of excretory response to such stimuli that the present study of renal function depends. Spaces are provided to chart the amounts of food not eaten by the patient, and corresponding allowances can be made in calculating the food intake. It is in no way essential that all the meals should be taken in their entirety, nor that the food should be exactly as indicated. The bill of fare here presented has been designed to adapt itself to the daily food supply furnished by the hospital. In private practice, it would only be necessary to ask the patient to eat three full meals a day and write down the approximate quantities, as—1 cup of coffee, 2 slices of toast, 2 tablespoonfuls of oatmeal, etc., in order to be certain that the diet for the day contained a sufficient quantity of the diuretic materials of our ordinary food to make an adequate demand on the kidney to test renal function. It is extremely desirable to insist on the fact that, since the food as found in most households suffices to carry out these tests and the procedure is not a complicated one, it need not be confined to hospitals and patients who can afford private nurses.

A wide variation may be permitted in the above-mentioned directions. Certain others, however, must be followed slavishly, in order to make the outcome of the test yield its maximum result. The urine must be collected punctually every two hours. No solid food or fluid of any kind must be taken between meals, and especial care must be observed that nothing of any kind is eaten or drunk during the night, and that the night specimen is completed before breakfast is touched. The reason for this is that the normal kidney responds rapidly to fluids ingested, so that within a few hours a marked diuresis occurs. The following observation may serve as an illustration of this previously well-established fact.

Time Interval	Urine Volume, c c	Fluid Ingested
6 p m - 8 p m	84	7 30 p m supper with 1,000 c c of water
8 p m - 10 p m	590	
10 p m - 8 a m	361	

In this instance, within two and one-half hours of drinking 1,000 c c of water, over 590 c c were eliminated, while during the eight-hour period following the diuresis, only 361 c c of urine were voided.

The volume in cubic centimeters and the specific gravity of each specimen collected are determined. At the outset of the investigation,

the salt and nitrogen² were measured in each specimen. It soon became apparent, however, that it was necessary to make these calculations only in the total day and night urines. The normal curves show agreement with one another in many respects, and are apparently divergent in others. A considerable number of tests were made on other normal individuals, but yielded nothing further than is known here. The important points to be noted are the following:

- 1 The characteristics of the day urine
- 2 The quantity of water, salt and nitrogen excreted in twenty-four hours

- 3 The characteristics of the night urine

These will be taken up in detail. The phenomena to be observed by means of the test meal may be obtained from specimens passed from day to day, and in patients who are involuntary or irrational, such piecemeal studies may become necessary. Although these have the disadvantage of being long drawn out and usually incomplete, it is surprising how many valuable data may be gleaned in this way, if the points to be noted are kept in mind.

THE NORMAL URINARY RESPONSE TO THE NEPHRITIC TEST MEAL

This is seen in Charts 1, 2, and 3 and Tables 1, 2, and 3. These three examples differ from one another in that the first subject is putting out an approximately normal quantity of fluid in relation to the amount of solids excreted, the second an abnormally large volume of urine (this individual, as a rule, took no tea or coffee and very little meat, the unaccustomed dose of purins of the test meal dietary, therefore, probably produced this great diuresis), the third, a subnormal quantity (a diminished amount of fluids being taken to note this effect). It should be borne in mind that the response to the nephritic test meal in normal individuals is practically always as in Charts 1 or 2. The type in Chart 3 may serve as a control for those pathological cases in which only a small amount of fluid is excreted. The facts to be noted are as follows:

In order to make the results of the test comprehensible at a glance, a graphic representation of the findings has been adopted, as shown in the accompanying charts (Charts 1 to 20 inclusive).

Explanation of the Charts—Each chart is divided by two horizontal lines into three tiers. The lowest of these gives the figures for water and specific

² The salt was estimated by the Volhard method, nitrogen by the Kjeldahl process. Where more extensive laboratory facilities are not at hand, the method of Strauss, as advocated by Bayne-Jones (*THE ARCHIVES INT MED*, 1913, *xii*, 90) for chlorids, and the hypobromid determination for urea will yield results that are easily obtained and are perfectly adequate from a practical point of view.

gravity, the middle for nitrogen and the upper for sodium chlorid. Each is further divided by a central vertical line into right and left halves. The left half, with its scale at the extreme left, contains six columns for the two-hourly specimens collected between 8 a m and 8 p m. Each column represents absolute values. The right half is read by the scale at the extreme right, whose divisions are usually equivalent to one-tenth of those on the left, but rarely, as in Chart 2, to one-fifth, to bring unusual figures within the compass of the chart. The columns of this right half are two pairs, separated by a space. The central pair represents the total night and the total day twelve-hour figures for volume, nitrogen and sodium chlorid, night in solid black and day in oblique hatching at its right. The pair at the extreme right represent intake and output for the whole twenty-four hours, intake at the left in vertical, output at the right in cross or oblique hatching. The dots joined by continuous lines crossing each tier from left to right indicate the specific gravity and the percentage concentrations of nitrogen and sodium chlorid, respectively, and are read from the scale at the left.

TABLE 1—NORMAL REACTION TO NEPHRITIC TEST MEAL

Time of Day	Urine		Sodium Chlorid		Nitrogen	
	cc	Sp Gr	Per Cent	gm	Per Cent	gm
8-10	153	1 016	1 32	2 02	0 89	1 26
10-12	156	1 019	1 25	1 95	0 74	1 15
12- 2	194	1 012	0 64	1 24	0 59	1 14
2- 4	260	1 014	0 77	2 00	0 56	1 46
4- 6	114	1 020	0 99	1 13	0 95	1 08
6- 8	238	1 010	0 43	1 02	0 52	1 23
Total day	1,115			9 36		7 32
Night, 8-8	375	1 020	0 63	2 36	1 23	4 61
Total 24 hours	1,490			11 72		11 93
Intake	1,760			8 5		13 4
Balance	+ 270			- 3 22		+ 1 47

Impression (the figures correspond with Chart 1) Normal reaction to the nephritic test meal. Note the variations occurring in the fluid output, and the specific gravity, which are in inverse ratio, the night urine, which is small in amount and shows a high specific gravity and a high percentage of nitrogen, and the approximately normal output of water, salt and nitrogen in twenty-four-hours.

TABLE 2—NORMAL REACTION TO NEPHRITIC TEST MEAL

Time of Day	Urine		Sodium Chlorid		Nitrogen	
	cc	Sp Gr	Per Cent	gm	Per Cent	gm
8-10	240	1 018				
10-12	482	1 010				
12- 2	244	1 019				
2- 4	290	1 010				
4- 6	120	1 017				
6- 8	420	1 007				
Total day	1,796		0 66	11 84	0 41	7 36
Night, 10-8	352	1 017	0 58	2 16	1 20	4 22
Total 24 hours	2,148			14 00		11 58
Intake	1,760			8 50		13 40
Balance	- 388			- 5 50		+ 1 82

Impression (the figures correspond with Chart 2) Normal reaction to the nephritic test meal. In this case, polyuria is evident. This is probably due to the reaction in an individual who is accustomed to a bland diet and not to the quantities of salt and purins taken with the test meal.

TABLE 3—NORMAL REACTION TO NEPHRITIC TEST MEAL

Time of Day	Urine	Sp	Gr	Sodium Chlorid		Nitrogen	
	c c			Per Cent	gm	Per Cent	gm
8-10	90	1 026		1 23	1 11	1 39	1 25
10-12	78	1 027		1 29	1 01	1 58	1 24
12- 2	114	1 027		1 27	1 45	1 30	1 48
2- 4	75	1 030		0 97	0 73	1 77	1 33
4- 6	85	1 030		1 20	1 01	1 66	1 42
6- 8	104	1 028		1 06	1 10	1 52	1 58
8-10	88	1 024		0 83	0 73	1 37	1 20
Total day	634				7 14		9 50
Night, 10-8	290	1 027		0 73	2 12	2 07	6 00
Total 24 hours	924				9 26		15 50
Intake	1,100				9 00		16 00
Balance	+ 176				- 0 26		+ 0 50

Impression (the figures correspond to Chart 3) Normal reaction to the nephritic test meal In this test the fluid was limited and the solid food increased, so as to produce a concentrated urine, as occurs in myocardial decompensation The characteristics of the normal response, rise of urine volume after each meal, the variation of specific gravity, the small volume of night urine with a high concentration of nitrogen and high specific gravity, and an approximate balance of fluid, salt and nitrogen, are all present in spite of the restrictions imposed (In this case supper was taken at 7 p m The collections of night urine were, therefore, begun at 10 p m instead of at 8 p m)

1 *The Day Urine*—Thus shows a rhythmical response to each meal in that the quantity of fluid increases at these periods This is well shown in Chart 3, in Charts 1 and 2 certain irregularities in the diuresis following food ingestion are seen In Chart 1 there is no distinct polyuria after breakfast and that after the mid-day meal occurs late A similar delayed polyuria is found on Chart 2 The diuretic response to each meal in the two-hourly periods was not as constantly present as Hedinger and Schlayer found it to be In fact, at times it is almost entirely suppressed, as is seen in the following instance, in which the rise of urine after supper is distinct, the other responses being masked or absent

Time of day	*8-10	10-12	*12-2	2-4	4*6	6-8
Volume of urine, c c	118	146	157	180	170	261

* Indicates the meal hours

Because of the irregularity of this symptom in normal cases, not very much stress has been laid on its absence in interpreting pathological urines However, a fixed or constant two-hourly output has proved itself to be of considerable significance in interpreting renal function in some patients

The specific gravity of the two-hourly specimens is not fixed, but varies inversely to the volume of urine, this is not as markedly the case in Chart 3, where the induced oliguria requires a urine of moderately constant high specific gravity in order to eliminate the required quan-

tity of solids. However, even in this case, the variations in specific gravity are by no means confined within one or two points, as they are in many of the pathological specimens. Table 4 gives a summary of these observations.

TABLE 4—SUMMARY OF SPECIFIC GRAVITY OBSERVATIONS IN NORMAL INDIVIDUALS

Case	Maximum	Minimum	Difference
1	1.020	1.010	10
2	1.019	1.007	12
3	1.031	1.024	7
4	1.019	1.009	10
5	1.020	1.007	13
6	1.025	1.005	20
7	1.023	1.010	13
8	1.018	1.008	10
9	1.018	1.007	11
10	1.019	1.007	12
11	1.026	1.014	12
12	1.030	1.010	20

The maximum and minimum figures for urinary specific gravity, as found in the specimens collected in two-hour periods during the day from normal individuals on a nephritic test diet. Note the marked variation between the highest and lowest observations in each instance. The lowest variation occurs in Case 3 (see Table 3), this is due to the fact that in this individual water intake was much restricted.

2 The Quantity of Water, Salt and Nitrogen Excreted in Twenty-Four Hours—Normally the urinary fluid output should be about 400 cc. less than the intake, to allow for the excretion of water by the lungs, skin and intestines. About 90 per cent. of the nitrogen ingested should be found in the urine, the remainder passing out in the feces. The sodium chlorid as found in the urine represents practically the total excretion of this substance except in cases of diarrhea. These statements hold true for carefully regulated metabolism studies carried on over several days, but it must be remembered that the previous habits have a very great bearing on tests such as those under consideration here. Thus it has been noted, on comparing Charts 1 and 2, how a full diet produces polyuria in an individual who has been accustomed to very bland food, and furthermore, it is found that a comparatively small amount of urine is produced by an individual who on the previous day has drunk too little fluid to meet his requirements. Various and often easily ascertainable reasons may exist for either retention or an excess of excretion, which may lead us to look on these phenomena as presenting no abnormalities. However, they should always be regarded with suspicion and be thoroughly considered in their bearing on the case in question. Vastly more important is the concentration of salt and nitrogen in the urine. A normal kidney can readily concentrate nitrogen and salt above 1 per cent., an abnormal kidney often

can not Therefore, the total quantity of urine and urinary ingredients excreted is to be observed, but particular stress is to be laid on the concentration of nitrogen and salt

3 *The Characteristics of the Night Urine*—Whatever the quantity of urine excreted during the day, it is found that the night specimen varies within very narrow limits The precautions of not allowing water at night time, previously dwelt on, must be strictly carried out to make this observation of value In the night urine, as a rule, the concentration of nitrogen and the specific gravity are high The figures for normals, as given in Table 5, substantiate these statements

TABLE 5—COMPARISON OF NIGHT AND DAY URINES IN NORMAL INDIVIDUALS
——Night Urine (12 Hours)—— Day Urine

Case	Specific Gravity	Nitrogen Per Cent	Volume c c	(12 Hours) Volume, c c
1	1 020	1 23	375	1,105
2	1 017	1 20	352	1,796
3	1 027	2 07	290	634
4	1 019	1 12	350	1,032
5	1 018	1 03	390	1,945
6	1 018	1 43	361	1,413
7	1 019	1 14	355	2,156
8	1 018	1 08	402	2 446
9	1 026	1 42	277	866
10	1 030	1 58	210	1,496
11	1 029	1 85	213	468
12	1 025	1 23	248	861

The nitrogen percentage, specific gravity and volume for the night urines of normal individuals on a nephritic test diet Note the high percentage of nitrogen, high specific gravity and the small volume of urine, as compared to the day specimen

The most important points to be observed in the urine of normal individuals on the nephritic test meal are

1 Variations in the specific gravity of the urine specimens (usually 10 points or more, in cases of diminished water intake and oliguria, the variations may be somewhat less)

2 The balance between the output and intake of salt, nitrogen and fluids This should be approximately equal

3 A night urine high in specific gravity (1 016, but usually 1 018 or higher), high in its percentage of nitrogen (above 1 per cent) and small in amount (400 c c or less), regardless of the quantity of fluid ingested or the amount of urine voided during the day

THE URINARY RESPONSE TO THE TEST MEAL IN DISEASE

The individual factors will be first discussed and then applied to special cases

1 *The Day Urine*—Koranyi³ summarized the essential findings of his own and others' work in relation to these problems. These are in full accord with the facts as substantiated by Hedinger and Schlayer¹ and in the present observations. The kidney expresses its diminished power to functionate by a fixation of its concentration. The normal kidney yields a urine of medium, low or high specific gravity (Table 4) according to the proportion of fluids and solids that must be excreted in order to maintain the composition of the body fluids at a constant level. The diseased kidney, on the other hand, loses this flexibility and the power to answer a demand for a more concentrated or more dilute urine no longer exists. This condition Koranyi has spoken of as hyposthenuria. Koranyi emphasizes the fact, which is usually not sufficiently appreciated, that the power to excrete a more dilute urine is lost, as well as that to concentrate (Chart 6). Such a fixation of specific gravity appears when the kidney is the seat of a nephritis, but the fact must not be lost sight of that extrarenal factors may damage kidney function to an equal extent. This fixation of specific gravity occurs in nephritis, pyelitis, cystitis associated with prostatic

TABLE 6—SPECIFIC GRAVITY OF URINES COLLECTED IN TWO-HOURLY PERIODS

Case	—Specific Gravity*—						Degrees of Variation in Readings
Normal (Chart 1)	16	19	12	14	20	10	10
Incipient primary contracted kidney	09	14	09	10	14	06	8
Incipient primary contracted kidney	18	09	16	22	13	10	11
Advancing primary contracted kidney	18	17	13	13	13	15	5
Advancing primary contracted kidney	19	20	20	20	21	20	2
Advanced primary contracted kidney	11	11	10	11	11	11	1
Advanced primary contracted kidney	12	11	11	11	12	13	2
Advanced primary contracted kidney	10	09	10	09	09	10	1
Advanced primary contracted kidney	05	06	07	08		08	3
Incipient chronic diffuse nephritis	25		24	33	28	30	9
Incipient chronic diffuse nephritis	09	16	15	17	12	07	10
Advanced chronic diffuse nephritis	12	11	14	11	13	11	3
Secondary contracted kidney	09	10	12	10	12	10	3
Congested kidney, myocardial decom- pensation marked	18	20	19	18	20	21	3
Congested kidney, moderate myocardial decompensation	25	24	24	25	24	21	4
Congested kidney, cardiac compensation, losing edema	12	15	10	15	13	10	5
Congested kidney, cardiac compensation, edema disappeared	05	06	11	09	09	10	5
Polycystic kidney	10	10	10	11	10	10	1
Marked anemia	10	10	10	10	10	11	1
Diabetes insipidus	04	04	06	04	04	04	2
Cystitis, pyelitis, prostatic hypertrophy	10	10	10	10	11	11	1
Pyonephrosis	11	12	12	13	12	12	2

* Variations of specific gravity in the day urine collected in two-hourly intervals. Note the fixed specific gravity of the severe cases of nephritis. Only the last two figures of each reading are given.

3 Koranyi and Richter "Physiologische Chemie und Medizin," Leipzig, 1908, 11, 136-152

hypertrophy, hydronephrosis, pyonephrosis, polycystic kidneys, renal congestion due to cardiac disease, both in the stage of decompensation and in the early stages of recovering compensation, diabetes insipidus, severe anemias, and possibly in other conditions

Table 6 shows the specific gravities of some of these urines, as found in the two-hourly diurnal periods

The figures in Table 6 bear out what has been said, and demonstrate how extreme a fixation of urinary concentration may become. In this connection the data given in Table 7 are also of interest, showing how a low specific gravity may remain a fixture from day to day in nephritis, in the diurnal as well as the nocturnal specimens

E F (Medical No 33757), male, aged 36. Albumin was discovered in the urine seventeen years ago. For five years there has been polyuria and polydipsia, for two years, failing vision. There is moderate thickening of all the peripheral arteries. The cardiac impulse is forcible in the fifth interspace, 12.5 cm to the left of the median line, indicating some hypertrophy of the heart muscle. There is no edema, nor are there other signs of myocardial insufficiency. The systolic blood pressure varies between 210 and 195 mm of mercury. The eyegrounds show marked albuminuric retinitis. The urine is large in amount, constantly low in specific gravity, contains about 1 gm of albumin per liter, and on microscopic examination yields a few hyaline casts. The phenolsulphone-phthalein excretion is 22 per cent in two hours. The nonprotein nitrogen of the blood is 59 mg per 100 cc. The diagnosis is an advanced degree of chronic diffuse nephritis (secondary contracted kidney).

The night and day urines followed over a considerable period gave the figures shown in Table 7.

TABLE 7—SHOWING THE CONSTANCY OF NOCTURNAL POLYURIA AND LOW SPECIFIC GRAVITY IN THE URINE OF A CASE OF ADVANCED CHRONIC DIFFUSE NEPHRITIS

Volume of Urine, c c		Urinary Specific Gravity *	
Day	Night	Day	Night
1,390	560	12	10
935	710	12	11
1,010	760	11	10
1,122	705	10	10
790	790	10	10
908	1,110	11	10
880	1,184	11	10
1,020	1,360	12	09
1,075	1,120	11	10
1,140	1,255	10	10
1,375	730	12	11
1,600	1,160	12	10
1,525	1,090	12	11
1,400	1,260	11	10
1,146	1,100	11	12
1,940	1,060	10	09
1,280	1,520	10	09
1,640	1,400	10	10
1,370	1,370	11	10
1,480	1,480	18	18
1,340	1,680	19	17
1,410	1,340	10	10
1,480	1,410	12	10
1,185	1,610	10	08

* Only two last figures are given

On two days (towards the lower portion of the table) the specific gravity rose to about 1.018. This is the only case of advanced nephritis with a tendency to low specific gravity in which a variation of this kind was noted. In chronic diffuse nephritis, such changes in the level of concentration are common, but they occur gradually, being associated with definite phases of the disease. (Compare Charts 17 and 18.) Von Noorden⁴ contends that all cases of contracted kidney pass a low specific gravity urine because of polydipsia, that they all concentrate the urine in some specimen during a part of the day, and that it is wrong to assume an obligatory hyposthenuria on their part. The figures of Table 6 indicate no variability in the day urine of these cases and all attempts to limit the water of such individuals have been found to be impracticable. The impression gained from these studies is that pathologic lesions of the kidney are responsible for the low fixed specific gravity of the urine and that, with rare exceptions, when once established it remains constantly low.

The level of the fixed specific gravity changes under certain conditions. Besides the cases of chronic diffuse nephritis just referred to, this is noted in myocardial insufficiency, in which it is constantly high (Charts 13 and 14), until compensation is established, when it assumes a lower level (Chart 15). Even then, when all edema has disappeared and it would be expected that the renal functions had returned to normal, this anomaly of urinary secretion, a low moderately fixed specific gravity, persists (Chart 16). It accentuates the fact that functional and anatomical integrity are not synonymous terms.

The water excretion is very often found to remain markedly constant in quantity in the two-hourly periods, as does the level of the specific gravity (Charts 6, 10, 11 and 12). This factor may be of value in estimating renal function, however, it was found to be of much less significance than the specific gravity in the tests here reported, and consequently the greatest stress has been put on the latter. The salt and nitrogen percentages of the urine exhibited the same tendency to a constancy in their percentage values as did the specific gravity figures. (Compare Charts 1, 2, and 3 of the normal individuals with Charts 7 and 11.) Here, again, nothing was added to the information gained from the specific gravity, and consequently, in order to simplify the whole procedure to its utmost, these determinations were omitted for the two-hourly specimens and ascertained only for the total day and night urines.

2 The Quantity of Water, Salt and Nitrogen Eliminated in Twenty-Four Hours—Impaired renal function may be associated with

⁴ Von Noorden. Handbuch der Pathologie des Stoffwechsels. Berlin, 1906, 1, 994.

a retention of one or all of these elements. The cardiac and renal cases have been rather fully investigated in this connection and, as a result, certain definite conclusions may be formulated in regard to them.

When there is passive congestion of the kidney due to myocardial insufficiency, the amounts of water and sodium chlorid eliminated are much diminished, while the nitrogen excretion remains approximately normal. An extreme case of this kind was found in L (Medical No 33177), who, on autopsy, proved to have cardiac decompensation, brought on by a severe grade of myocarditis, thromboses of the coronary arteries and infarcts in the myocardium, the kidneys showed congestion only, urinary tests in this patient yielded the results shown in Table 8.

TABLE 8—RESULTS OF URINARY TESTS IN PATIENT L
(MARKED MYOCARDIAL INSUFFICIENCY)

Day	Urine Volume, c c	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
1	850	1.022	0.02	0.17	1.76	14.9
2	770	1.022	0.04	0.31	1.74	13.4
3	545	1.025	0.03	0.16	1.56	8.5
4	420	1.025	0.02	0.08	1.56	6.6

In such instances, the minimal concentration of salt and the high percentage of nitrogen indicate the very limited ability of the kidney to eliminate sodium chlorid, while the power to excrete nitrogen remains normal, provided a reasonable amount of urine is secreted.

Milder grades of myocardial decompensation yield similar results, though the sodium chlorid elimination is not diminished to the same extent. This is well shown in Charts 13 and 14. These and two similar cases may be summarized in Table 9.

TABLE 9—SUMMARY OF URINE TESTS IN CASES OF MYOCARDIAL
DECOMPENSATION

Case	Urine Volume, c c	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
1	540	1.020	0.25	1.34	1.44	7.78
2	573	1.019	0.28	1.62	1.76	10.08
3	484	1.022	0.52	2.53	1.58	7.64
4	446	1.018	0.61	2.72	1.38	6.15

The low percentage of salt and the oliguria, as compared to the high concentration of nitrogen, are very strikingly shown in Table 9.

With recovery of cardiac compensation, the excretion of salt and water is much improved, as is seen in Charts 15 and 16. Many of these individuals, however, do not excrete the salt of their dietary completely. Retaining a small amount of salt on each day, they finally develop a marked edema. Under these circumstances, the curious picture often presents itself of a patient with general subcutaneous

edema, and possibly a transudate in one or the other of the body cavities, without dyspnea, marked cyanosis, or other signs of myocardial insufficiency. On the removal of salt from the food, the edema again disappears rapidly. Not all cases exhibit this inability to excrete sodium chlorid. Except by trial, there seems to be no way of distinguishing those that will from those that will not tolerate salt. It is a very important point, from the therapeutic side, and as much stress should be laid on the restriction of salt in these cases as on the limitation of fluids.

In nephritis, two distinct types of excretion are found

1 Salt retention not associated with deficient nitrogen elimination. This is seen in the cases of chronic diffuse (parenchymatous) nephritis. The entire picture has had Widal's name associated with it for a long time. A test meal in a patient of this type yields the results shown in Table 10.

TABLE 10—NEPHRITIC TEST MEAL IN A CASE OF CHRONIC DIFFUSE (PARENCHYMATOUS) NEPHRITIS

Time of Day	Urine cc	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	32	1.025				
10-12	0					
12-2	54	1.024				
2-4	64	1.033				
4-6	64	1.028				
6-8	66	1.030				
Total day	280		0.18	0.50	1.91	5.34
Night, 8-8	595	1.016	0.08	0.48	0.93	5.53
Total 24 hours	875			0.98		10.87
Intake	1,760			8.50		13.40
Balance	+ 885			+ 7.52		+ 2.53

Impression. There is marked salt and water retention, the excretion of nitrogen is adequate. The variations in specific gravity distinguish this case from one of cardiac insufficiency, and indicate that renal function as a whole is not seriously impaired.

With rest and adequate treatment, the power to excrete salt and water is rapidly acquired, and the whole process of renal activity changes. A test meal in the same individual yields an entirely different set of figures under such circumstances (Table 11).

2 In advanced cases of primary or secondary contracted kidney, characterized by hypertension and termination in uremia, the quantities of salt and nitrogen excreted are both diminished. In none of these patients has much improvement in this regard been noted. In observing the urine of hypertensive nephritis, and attempting to couple it with constant clear-cut characteristics, the precaution must be taken to separate the uncomplicated cases from those associated with other

lesions, such as marked anemia, cardiac insufficiency, or bronchopneumonia. The analyses of the test meals in these individuals, all of them in advanced stages of the disease, are shown in Table 12.

TABLE 11—NEPHRITIC TEST MEAL IN THE SAME CASE AS TABLE 10—
SOME TIME LATER

Time of Day	Urine cc	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	137	1.015	0.82	1.12	0.70	0.95
10-12	148	1.016	0.82	1.11	0.80	1.18
12- 2	108	1.016	0.78	0.84	0.79	0.85
2- 4	184	1.015	0.57	1.04	0.79	1.46
4- 6	96	1.015	0.48	0.46	0.79	0.76
6- 8	470	1.004	0.30	1.45	0.25	1.18
Total day	1,143			6.02		6.38
Night, 8-8	960	1.010	0.34	3.26	0.38	3.65
Total 24 hours	2,103			9.28		10.03
Intake	1,760			8.50		13.40
Balance	-343			-0.78		+3.37

Impression. Water and salt are excreted in excess in contrast to previous meal. The polyuria, both during the day and night, and the rather low fixed specific gravity, are due to the fact that this patient is eliminating edema, and must not be confounded with similar curves obtained in case of hypertensive nephritis, where they would indicate a considerable degree of impaired renal function. On physical examination, the two conditions can very easily be distinguished from one another.

TABLE 12—NITROGEN, SALT AND WATER EXCRETION IN ADVANCED
UNCOMPLICATED INTERSTITIAL NEPHRITIS *

Case	Urine Volume, cc	Specific Gravity	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
1	776	1.014	0.37	2.88	0.65	5.08
2	1,282	1.013	0.29	3.69	0.52	6.71
3	1,276	1.012	0.42	5.41	0.49	6.28
4	1,535	1.009	0.35	5.34	0.42	6.51
5	1,873	1.011	0.41	7.64	0.14	2.59
5	1,541	1.010	0.30	4.70	0.30	4.64
7	1,665	1.009	0.12	2.00	0.09	1.50

* The approximate intake was 1,760 cc of fluid, 8.5 gm of salt and 13.4 gm of nitrogen in each case.

From Table 12 it is clear that the low specific gravity usually attributed to these cases has been found here as well, and that the urinary concentration of salt and nitrogen is so much depressed that there is retention of these substances.

When cases of this kind are complicated by various intercurrent factors, the same degree of impairment in the elimination of salt and water is not found even just before death. Fatal termination in them is hastened by anemia, heart failure, bronchopneumonia, etc., and hence the involvement of renal function does not have an opportunity to develop to its full extent. It may be that the lack of a uniform

picture in the urine of uremic patients (and even renal cases less severely affected) may be due to the tendency to place every case of hypertension in this category, regardless of whether any complications be present or not

In no instance has the combination of nitrogen retention with sufficient salt excretion been met with

3 *The Night Urine*—Since the systematic and thorough observations of Quincke,⁵ it has been recognized that a nocturnal polyuria is a valuable sign of impaired renal function. Through these, and the studies of v Leube,⁶ Runeberg,⁷ Wilson,⁸ Iljisch,⁹ Laspeyres¹⁰ and Pehu,¹¹ it has been shown that a supernormal quantity of urine at night, or nycturia, as it has been termed by Pehu, is significant of a variety of conditions. Acute or chronic nephritis, amyloid kidney, myocardial insufficiency, diabetes mellitus, cystitis, prostatic hypertrophy, and the excretion of edema, have all been found at times to produce a nycturia.

It is often noted in patients' histories that urine is voided two, three or more times during the night, and yet closer investigation shows this to be a nocturnal pollakiuria, not accompanied by an increase above the normal amount (400 c c). In some cases, a urethritis, prostatic hypertrophy or other local source of irritation may be found, in others, constituting a large number, the increased frequency of voiding at night can only be attributed to a nervous habit. Among many investigated with this point in view, the following may serve as an example. The patient complained of voiding four to ten times a night before admission, since entering the hospital he has passed his urine three or more times. In two twenty-four-hour periods the day urine amounted to 742 and 510 c c, the night specimens to 202 and 315 c c. To interpret the increased frequency of voiding urine at night as signifying a nocturnal polyuria, as is often done, would in such cases lead to an erroneous conclusion.

In the course of these studies,¹² the impression has been gained that nycturia is frequently one of the earliest symptoms of renal disease

5 Quincke Arch f exper Path u Pharmacol, 1913, xxxii, 211

6 Von Leube Deutsch Arch f klin Med, 1869, v, 372

7 Runeberg Deutsch Arch f klin Med, 1880 xxvi, 211

8 Wilson Lancet, London, 1889, I (67th year), 1299

9 Iljisch Munchen med Wchnschr, 1896, xciii, 1299

10 Laspeyres Deutsch Arch f klin Med, 1900, lxxviii, 175

11 Pehu Rev de méd, 1903, xxiii, 379

12 In collecting separate night and day specimens, the precautions previously mentioned, that supper be taken three hours before the night urine collection is begun, that no food or fluid be allowed during the night, and that the night specimen be completed before breakfast is eaten, have been strictly observed throughout

met with It may be found when the only other signs of nephritis are a trace of albumin and a few hyalin casts Thus, in W (Medical No 34121), a laborer of 23 years, showing a trace of albumin and a moderate number of hyalin and granular casts in the urine, but no other signs of nephritis, the figures shown in Table 13 were obtained after the test meal

TABLE 13—NEPHRITIC TEST MEAL IN AN INDIVIDUAL WITH A SLIGHT GRADE OF ALBUMINURIA, A FEW CASTS, BUT NO OTHER SIGNS OF NEPHRITIS

Time of Day	Urine cc	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	65	1 020				
10-12	67	1 021				
12- 2	90	1 020				
2- 4	126	1 019				
4- 6	146	1 015				
6- 8	172	1 013				
Total day	666		0 64	4 26	1 05	6 99
Night, 8-8	660	1 011	0 52	3 43	0 71	4 69
Total 24 hours	1,326			7 69		11 68
Intake	1,760			8 50		13 40
Balance	+ 434			+ 0 81		+ 1 72

Impression The concentration of urine, as indicated by the specific gravity and the percentage figures of sodium chlorid and nitrogen, are satisfactorily high The total amounts of fluids and solids eliminated may also be considered normal However, the urinary volume and specific gravity do not vary after the ingestion of meals as they should, and the night urine shows a distinct nocturnal polyuria with a low specific gravity The whole picture, therefore, represents a moderately impaired renal function

Occasionally, nocturnal polyuria is found in cases in which no organic cause for this phenomenon can be determined It may be that in these patients an augmented night urine represents a functional change which exhibits itself as the first symptom of a kidney lesion This is a surmise, and can be proved only by noting the subsequent course of events One such case is as follows

S C (Medical No 33538), aged 38, a valet, has had several attacks of acute gout The patient's joints show signs of the process, which has left permanent damage in the knees and some of the smaller joints of the feet, the urine is

TABLE 14—DATA IN A CASE OF NOCTURNAL POLYURIA WITHOUT DEMONSTRABLE RENAL INVOLVEMENT

Night Urine			Night Urine		
Specimen	Vol cc of Night Urine	Sp G of Night Urine	Specimen	Vol cc of Night Urine	Sp G of Night Urine
No			No		
1	347	1 026	6	692	1 017
2	664	1 018	7	550	1 025
3	980	1 011	8	990	1 016
4	680	1 020	9	1,214	1 014
5	961	1 015			

negative for albumin and casts, the systolic blood pressure is 123, the phenol-sulphonephthalein excretion is 80 per cent in two hours. No signs of nephritis can be detected, though the frequent association of gout and damage to the kidney are kept in mind. The test meal shows a normal function, except for a nocturnal polyuria. This is duplicated on subsequent nights and the figures in Table 15 are obtained.

With the exception of the first specimen, the volume at night is distinctly increased above the normal (400 c c). The specific gravity (except in Specimen 3) is, however, not as low as is usual in pathological night urines. It may well be that in the very earliest stages of diminished renal function the amount of urine is increased without a lowering of the specific gravity. This also goes to show that the low specific gravity need not necessarily follow on the passage of a large volume of urine at night, but depends to some extent on other factors.

TABLE 15—VOLUME, SPECIFIC GRAVITY AND NITROGEN PERCENTAGE OF THE NIGHT URINE IN CASES OF CHRONIC INTERSTITIAL NEPHRITIS *

Night Urine			Night Urine		
Volume c c	Specific Gravity †	Per Cent Nitrogen	Volume c c	Specific Gravity †	Per Cent Nitrogen
1,273	09	0.28	550	10	0.63
1,140	07	0.20	546	12	0.65
1,140	10	0.43	546	17	0.68
1,110	10	0.61	520	13	0.63
1,080	07	0.23	510 ‡	18	1.05
1,010	10	0.42	505	15	0.55
965	11	0.65	446 ‡	20	1.08
935	10	0.50	445	10	0.50
875	10	0.55	445	10	0.72
870	11	0.15	435	16	0.51
790	10		425 ‡	17	0.97
770	15	0.57	415	15	0.76
715	16	0.71	395	14	0.68
704	11	0.47	370	13	0.55
690	13	0.57	360	11	0.87
660	11	0.71	355 §	24	0.93
654	13	0.57	293 §	28	1.04
590 ‡	20	1.30	144	19	0.87
559	12	0.92	94	15	0.51
557	13	0.70			

* Includes all cases of chronic interstitial nephritis studied, many of them associated with hypertension and arteriosclerosis, but not complicated by myocardial insufficiency, a febrile process, marked anemia, or other intercurrent affection.

† Last two figures only.

‡ These cases may be considered as approaching the normal, from the night urine alone, only a very slight degree of impairment of renal function is evident.

§ Normal night urines, both of these cases are taken up in detail further on.

Besides the actual increase in the volume of night urine, changes in the specific gravity and concentration of nitrogen have proved themselves of importance in indicating impaired renal function. In Table 15 a considerable number of instances are given in which the night urine is normal in amount, or approximates the normal, and yet the

specific gravity findings are low and the concentration of nitrogen does not reach the normal

It is a well established fact that nitrogen derived from the food is excreted rather slowly,¹³ hence the quantity of nitrogen found in the night urine is disproportionately high. This has been shown to be

TABLE 16—TYPES OF CASES OTHER THAN CHRONIC INTERSTITIAL NEPHRITIS, WHOSE URINE GIVES EVIDENCE OF ABNORMAL NOCTURNAL EXCRETION

	Night Urine		
	Volume c c	Specific Gravity *	Per Cent Nitrogen
1 Chronic diffuse nephritis during			
(a) Water Retention (edema formation)	595	16	0.93
	553	16	0.62
	367	20	0.88
	270	30	
	106	28	
(b) Elimination of edema	960	11	
	960	10	0.47
	950	14	0.73
(c) Water balance (edema eliminated)	865	13	0.75
	490	14	1.01
	400	17	1.17
2 Heart disease during			
(a) Myocardial decompensation	275	21	1.85
	172	21	1.67
	119	25	1.82
	91	20	1.68
(b) Elimination of edema	1,340	11	0.51
	990	13	0.56
	850	10	0.28
	720	07	0.35
(c) Water balance (edema eliminated)	520	14	0.84
	515	11	0.53
	438	12	0.67
3 Hypertensive nephritis, complicated by myocardial decompensation	815	18	0.94
	546	17	0.68
	435	16	0.51
	405	18	1.07
	350	19	1.12
	108	18	1.09
4 Severe anemia	1,250	10	0.51
	680	10	0.52
	256	11	0.57
	180	16	0.39
5 Cystitis and hypertrophied prostate gland	1,395	09	0.43
	1,146	10	0.35
	775	11	0.44
6 Pyelonephritis	950	10	0.45
7 Polycystic kidney	1,290	10	0.45
8 Diabetes insipidus	594	07	0.20

* Last two figures only

constantly above 1 per cent in normal subjects, whereas, in Table 15, it is seen how low it has a tendency to become in cases of chronic nephritis, even when there is no nocturnal polyuria. The value of the specific gravity determinations in the night urine depends on similar principles of loss of power of concentration on the part of the diseased kidney.

Similar disturbances in nocturnal urinary secretion are seen in other conditions besides chronic interstitial nephritis. The list of these diseases is a considerable one (Table 16), and a consideration of them leads to the conclusion that renal function may be impaired, so far as the night urine is concerned, by a variety of factors. These same influences also modify the diurnal character of the urine, and they can be discussed to the greatest advantage in taking up the test meal as an entity.

THE RESULTS WITH COMPLETE NEPHRITIC TEST MEALS

Chronic Interstitial Nephritis (Primary or Secondary Contracted Kidney)—It must be borne in mind in studying renal function by means of a test meal or other procedure that anatomical lesions and changes in physiological activity of the organ need not parallel one another. This is particularly true of incipient nephritis, in advanced stages, when much of the renal parenchyma has been destroyed, divergence between autopsy findings and functional tests or clinical symptoms are far less marked. When only a limited amount of functioning renal tissue remains, the reserve power of the kidney and thus its ability to vary its activity within wide limits, is obviously restricted. It becomes necessary for such quantitatively reduced kidneys to function constantly at their maximum capacity, with the result that the urines secreted scarcely vary in their characteristics from day to day or even from hour to hour.

Examining the test meals of these advanced cases (Table 17, Chart 7), the hyposthenuria, as exhibited in the almost absolute fixation of the percentage figures for salt and nitrogen concentration and the specific gravity (Table 6) show under what continual strain the kidney is laboring to eliminate a sufficient quantity of solids. Even through polyuria it cannot keep pace with the food intake (Table 12). A still greater degree of retention, coupled with a more dilute urine, is seen in Chart 8 (Table 18). Many instances were obtained similar to the former, but only one more marked case of renal insufficiency has thus far been encountered, and that is the one pictured here (Chart 8). Both of these patients died within a few weeks after the test was taken, and the same bad prognosis proved itself correct whenever a test meal curve of this nature was produced. The points

indicating renal insufficiency in these severe examples of contracted kidney are the following

- 1 Markedly fixed and low specific gravity
- 2 Diminished output of both salt and nitrogen
- 3 Tendency to total polyuria
- 4 Night urine showing slight or marked increase in volume, low specific gravity, low concentration of nitrogen

TABLE 17—REACTION TO NEPHRITIC TEST MEAL IN ADVANCED HYPERTENSIVE NEPHRITIS

Time of Day	Urine cc	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	133	1 010	0 36	0 48	0 35	0 47
10-12	176	1 009	0 36	0 63	0 34	0 60
12- 2	156	1 010	0 32	0 50	0 35	0 55
2- 4	212	1 009	0 36	0 76	0 34	0 72
4- 6	164	1 009	0 38	0 62	0 36	0 59
6- 8	104	1 010	0 33	0 34	0 33	0 34
Total day	945			3 33		3 27
Night, 8-8	590	1 010	0 34	2 01	0 38	2 24
Total 24 hours	1,535			5 34		5 51
Intake	1,510			5 80		12 20
Balance	— 25			+ 0 46		+ 6 69

Impression (the figures correspond with Chart 7) Reaction to the nephritic test meal in a case of advanced hypertensive nephritis. There is very marked fixation of the percentage figures for nitrogen and salt concentration and the specific gravity. There is evident nitrogen retention. The salt intake is too low to make it certain that a diminished ability to excrete salt does not exist.

TABLE 18—EXTREME INTERSTITIAL NEPHRITIS

Time of Day	Urine cc	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	24	1 005				
10-12	106	1 006				
12- 2	82	1 007				
2- 4	83	1 008				
4- 6	0					
6- 8	230	1 008				
Total day	525		0 12	0 63	0 25	1 28
Night, 6-8	1,140	1 007	0 12	1 37	0 20	2 27
Total 24 hours	1,665			2 00		3 55
Intake	1,850			6 00		13 00
Balance	+ 185			+ 4 00		+ 9 45

Impression (the figures correspond with Chart 8) Reaction to the nephritic test meal in a case of extreme interstitial nephritis. Note the low fixed specific gravity, the retention of salt and nitrogen, and the night urine, which is increased in amount, shows a low specific gravity and a low nitrogen concentration.

Tracing the progress from the normal towards this ultimate stage, patients are found in whom a nocturnal polyuria persists, and yet there is no demonstrable affection of any kind in the kidney. Obser-

vations on such a case have been previously given in this paper. It is probable that these are the signs of a beginning nephritis exhibiting itself by slight changes in function. On the other hand, normal functional tests may be obtained when albumin and a few hyalin casts exist in the urine and there is a slight rise in blood pressure. An example of this kind is shown in Table 19, Chart 4, where the only

TABLE 19—COMPARATIVELY NORMAL RENAL FUNCTION IN EARLY HYPERTENSIVE NEPHRITIS

Time of Day	Urine c c	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	60	1 018				
10-12	140	1 009				
12- 2	156	1 016				
2- 4	58	1 022				
4- 6	252	1 013				
6- 8	122	1 010				
Total day	788		0 52	4 10	0 52	4 10
Night, 8-8	355	1 024	0 71	2 51	0 93	3 30
Total 24 hours	1,143			6 61		7 40
Intake	1,760			8 50		13 40
Balance	+ 617			+ 1 89		+ 6 00

Impression (the figures correspond with Chart 4) Except for a diminished nitrogen output and a slightly lowered nitrogen concentration at night, the response to this nephritic test meal is normal. It indicates a comparatively normal renal function in an early case of hypertensive nephritis.

TABLE 20—EARLY HYPERTENSIVE NEPHRITIS

Time of Day	Urine c c	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	465	1 009	0 51	2 37	0 34	1 58
10-12	102	1 014	0 62	0 63	0 77	0 79
12- 2	205	1 009	0 32	0 66	0 44	0 90
2- 4	160	1 010	0 28	0 44	0 64	1 02
4- 6	116	1 014	0 48	1 55	0 80	0 92
6- 8	160	1 006	0 09	0 14	0 29	0 46
Total day	1,208			4 79		5 67
Night, 8-8	935	1 010	0 33	3 08	0 50	4 67
Total 24 hours	2,143			7 87		10 34
Intake	1,760			7 50		13 40
Balance	- 383			- 0 37		+ 3 06

Impression (the figures correspond with Chart 5) The nephritic test meal shows a tendency toward fixation of specific gravity and a distinct nocturnal polyuria in an early case of hypertensive nephritis.

sign of diminished function exists in the slightly lowered concentration of nitrogen (0 93 per cent at night instead of a normal of 1 per cent or higher), and a moderate nitrogen retention. These changes are so slight as to make it doubtful whether it is not best to classify this

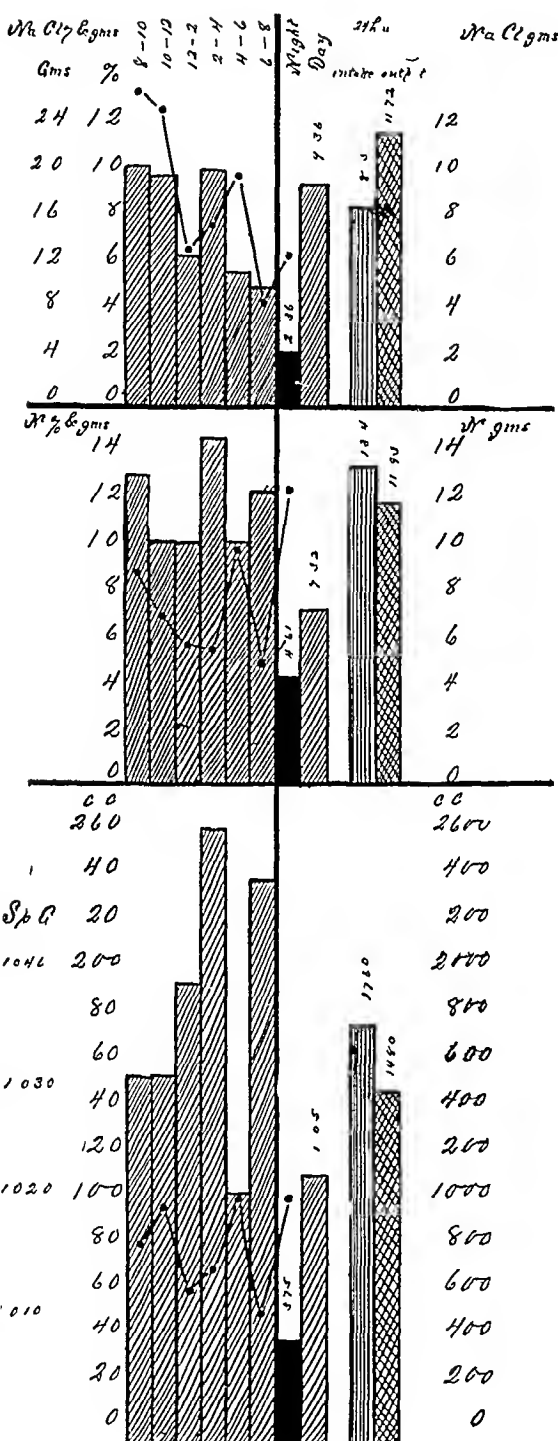


Chart 1

Chart 1—Normal Note the variations in specific gravity, high specific gravity and high concentration of nitrogen at night, and approximately normal water, salt and nitrogen output

Chart 2—Normal Same as Chart 1, except that in this case polyuria is evident This is probably due to the reaction in an individual who is used to a bland diet and not to the quantities of salt and purins given with the nephritic test meal

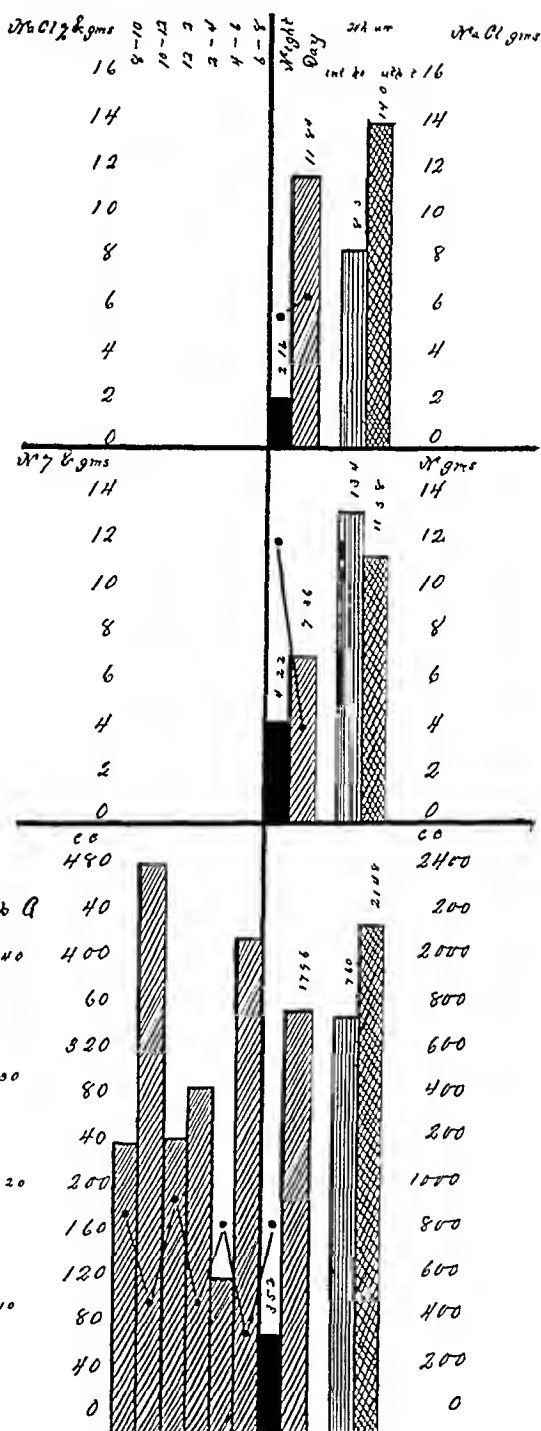


Chart 2

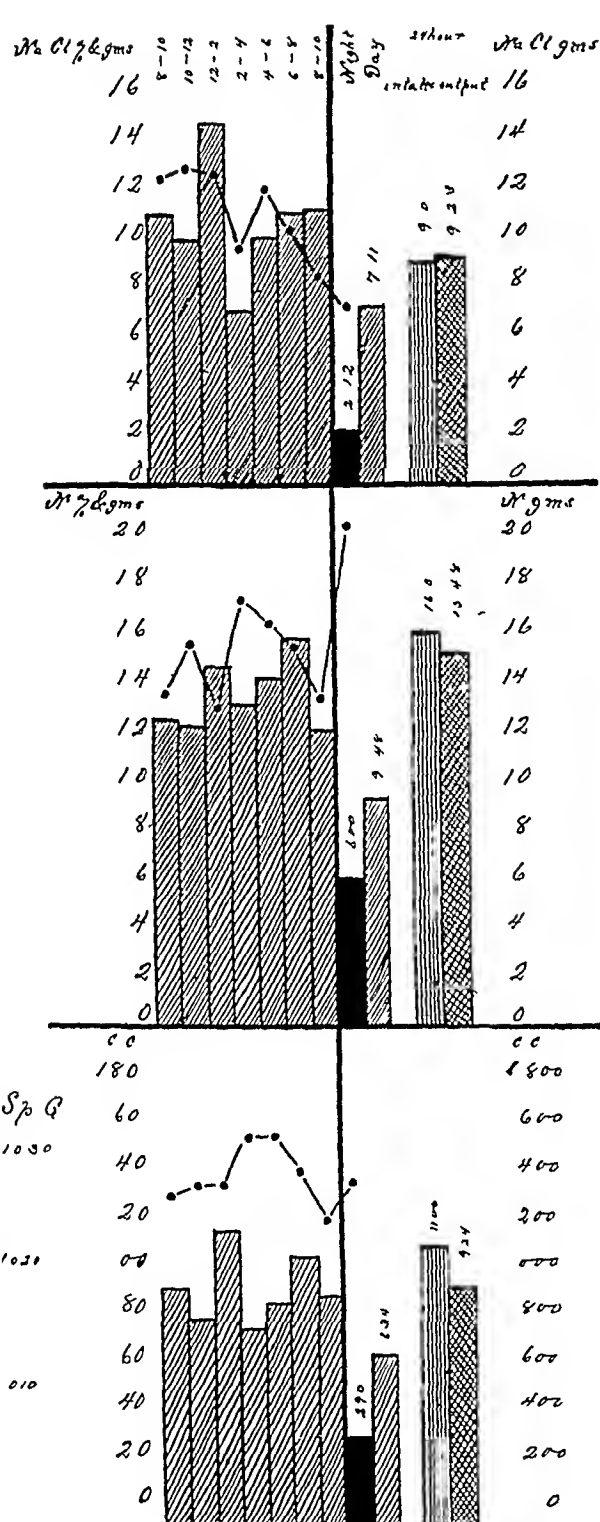


Chart 3

Chart 3—Normal Showing the effect of diminished fluid intake

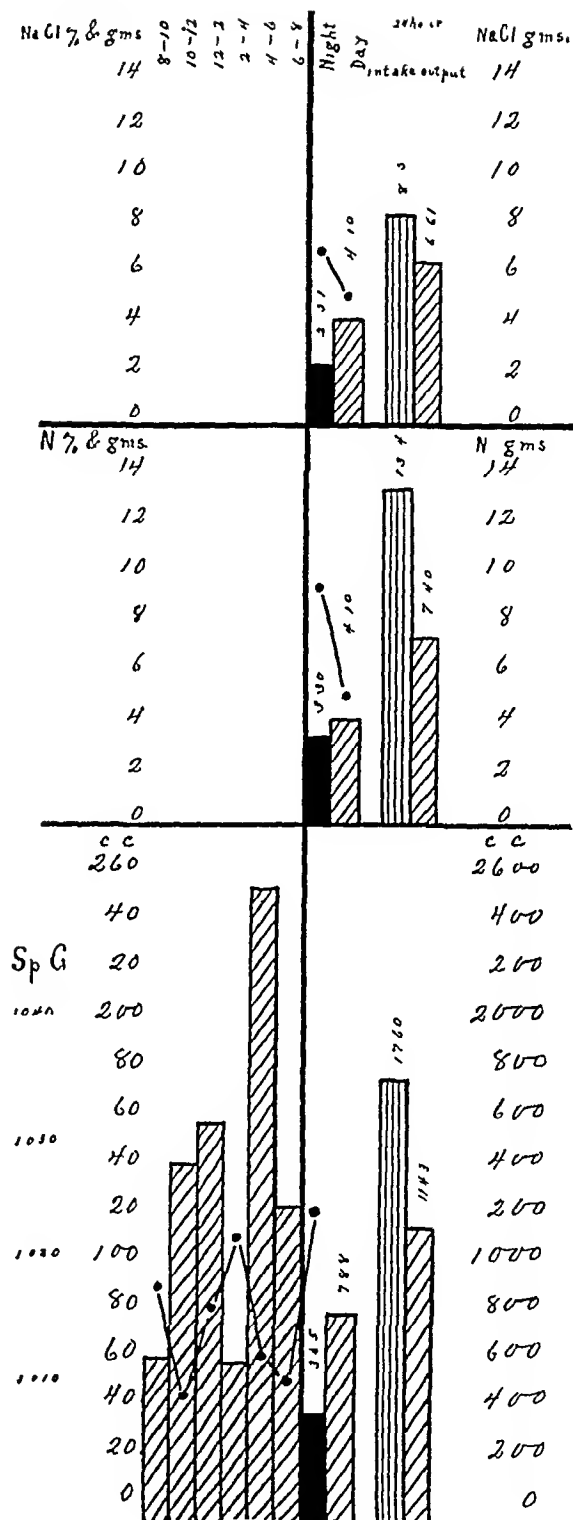


Chart 4

Chart 4—Early case of hypertensive nephritis (Systolic blood pressure 180, when up and about, 145 after rest in bed. Urine shows a trace of albumin and a few hyaline casts) Nephritic test meal is normal, except for a slight grade of nitrogen retention

test as a completely normal one, especially as the variations in specific gravity in the two-hourly specimens are marked, there is a good response of water excretion to dinner and supper, the salt elimination is adequate, and the night urine shows neither increased amount nor lowered specific gravity. Successive advances in impairment of renal function are seen in the tests depicted in Table 20, Chart 5, and in Table 21, Chart 6.

TABLE 21 —HYPERTENSIVE NEPHRITIS

Time of Day	Urine cc	Sp Gr	(Sodium Chlorid)		(Nitrogen)	
			Per Cent	gm	Per Cent	gm
8-10	172	1 019	0 95	1 63	1 01	1 74
10-12	154	1 020	0 99	1 52	0 87	1 34
12- 2	124	1 020	0 84	1 04	0 51	0 63
2- 4	110	1 020	0 74	0 81	0 93	1 03
4- 6	152	1 021	0 85	1 29	0 62	0 93
6- 8	143	1 020	0 72	1 03	1 11	1 59
Total day	855			7 32		7 26
Night, 8-8	446	1 020	0 97	4 33	1 08	4 82
Total 24 hours	1,301			11 65		12 08
Intake	1,760			8 50		13 40
Balance	+ 459			-3 15		+ 1 32

Impression (the figures correspond with Chart 6) Nephritic test meal in a case of marked hypertensive nephritis. The fixation of specific gravity at a level somewhat higher than that seen in more advanced cases of hypertensive nephritis is very striking.

In the former of these, the specific gravity fluctuates between narrower limits than normal, there is distinct polyuria, the night urine is increased in amount and shows a low specific gravity and low nitrogen concentration. In the second case, the fixation of specific gravity is striking, though its level is higher (1 020) than that seen in the more advanced stages of the disease (1 010). This phenomenon is not commonly seen in nephritic individuals, and when it does occur, the possibility of renal congestion, depending on myocardial decompensation, must be kept in mind. However, the oliguria, coupled with a very low salt output and a high nitrogen excretion in cardiac cases, usually distinguishes such urines from one another without difficulty. The changes that are brought about in the urine by the functional impairment occurring in the course of development of an interstitial nephritis may be formulated in the following manner, though this order of events will not pertain in every case. In the main, it portrays facts as they are usually encountered.

1 Nocturnal polyuria (over 400 cc)

2 Tendency to total polyuria (the volume of urine equals or surpasses the quantity of liquids ingested)

3 Fixation of specific gravity, gradually becoming more intense, until it is absolute and the specimens only show a maximum variation of 1 or 2 degrees. In the earlier stages, specific gravity may be fixed at a higher level than later.

4 Fixation of the two-hourly quantities of urine eliminated. That is, the usual polyuric response to meals is absent.

5 The quantity of night urine may diminish to within normal limits. Such night urines, however, are characterized by a low specific gravity and a low percentage of nitrogen.

6 A retention of both salt and nitrogen, which may become very marked.

Cases Simulating the Mode of Urinary Output Found in Advanced Nephritis—In cases of hypertrophied prostate and its sequelae, of pyelonephritis, polycystic kidney and severe anemia, whether of the primary or secondary type, results are obtained with the test meal which are similar in every detail to those that have been described for advanced instances of contracted kidney. These are shown in Charts 9, 10, 11 and 12.

These observations make it clear that the low fixed specific gravity, etc., so characteristic of advanced cases of hypertensive nephritis may be reproduced by widely different causes. These may be summarized as follows:

1 Causes in the urinary passages, pyelitis, cystitis, hypertrophied prostate.

2 Causes in the blood, marked anemia.

3 Causes in the kidney itself (organic as well as functional lesions), pyelonephritis, polycystic kidney, chronic interstitial nephritis (both primary and secondary contracted kidney), diabetes insipidus.

It is true that changes resembling those mentioned above are found in congestion of the kidney and in chronic diffuse nephritis (before the picture of contracted kidney supervenes), although there are certain variations from the type just depicted that are of material aid in diagnosing and treating these cases that will be detailed a little further on. It is interesting to note how very different the influences are that result in similar changes in function. From the functional change alone one would be warranted in considering the prognosis grave. Hence it must be emphasized that, when such evidence of functional damage is obtained, searching examination must be made for extrarenal causes or curable renal lesions, especially a hypertrophied prostate or other cause for urinary obstruction. Prognosis and therapy will depend largely on the cause of the functional impairment, not on its degree. The removal of a hypertrophied

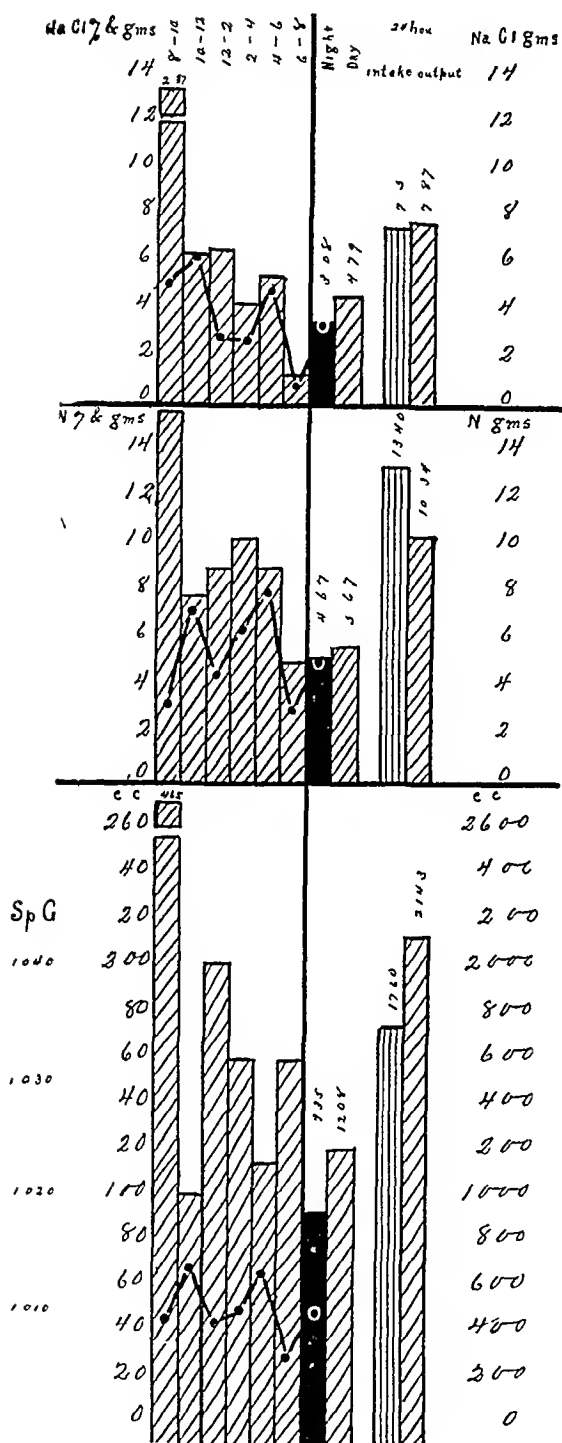


Chart 5

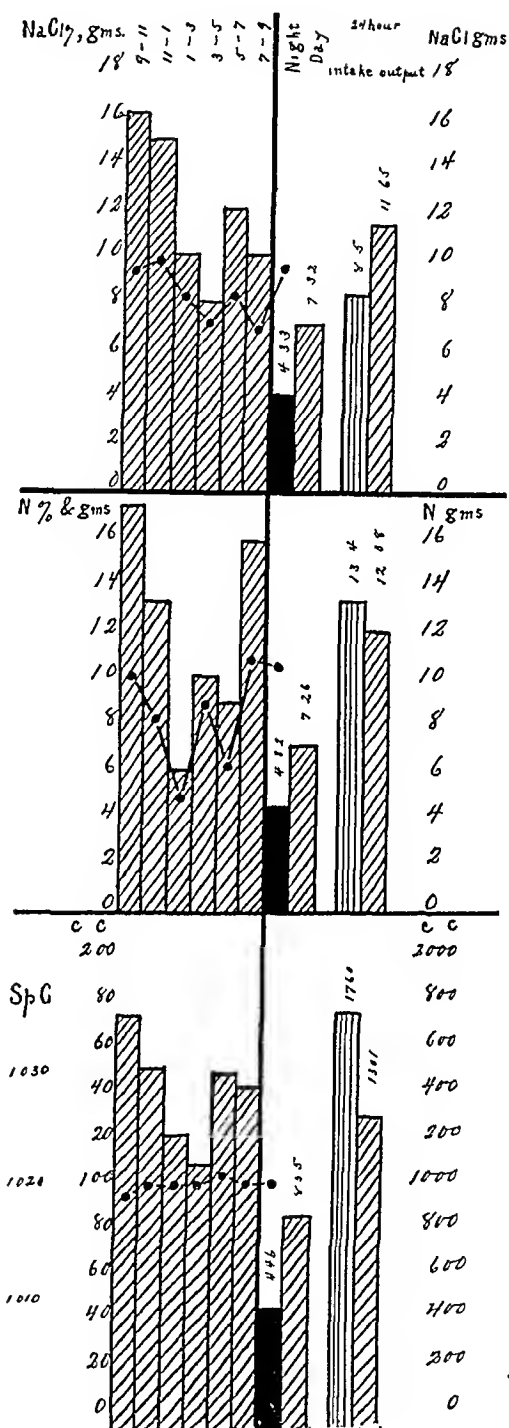


Chart 6

Chart 5—Early case of hypertensive nephritis (Systolic blood pressure, 160-190 Urine shows faint trace of albumin and a few granular casts) Nephritic test meal here shows a tendency towards the fixation of specific gravity and distinct nocturnal polyuria

Chart 6—Marked hypertensive nephritis (Blood pressure, 180 Urine shows trace of albumin and a few hyaline casts) Nephritic test meal shows markedly fixed specific gravity at a somewhat higher level than the more extreme cases shown in Charts 7 and 8

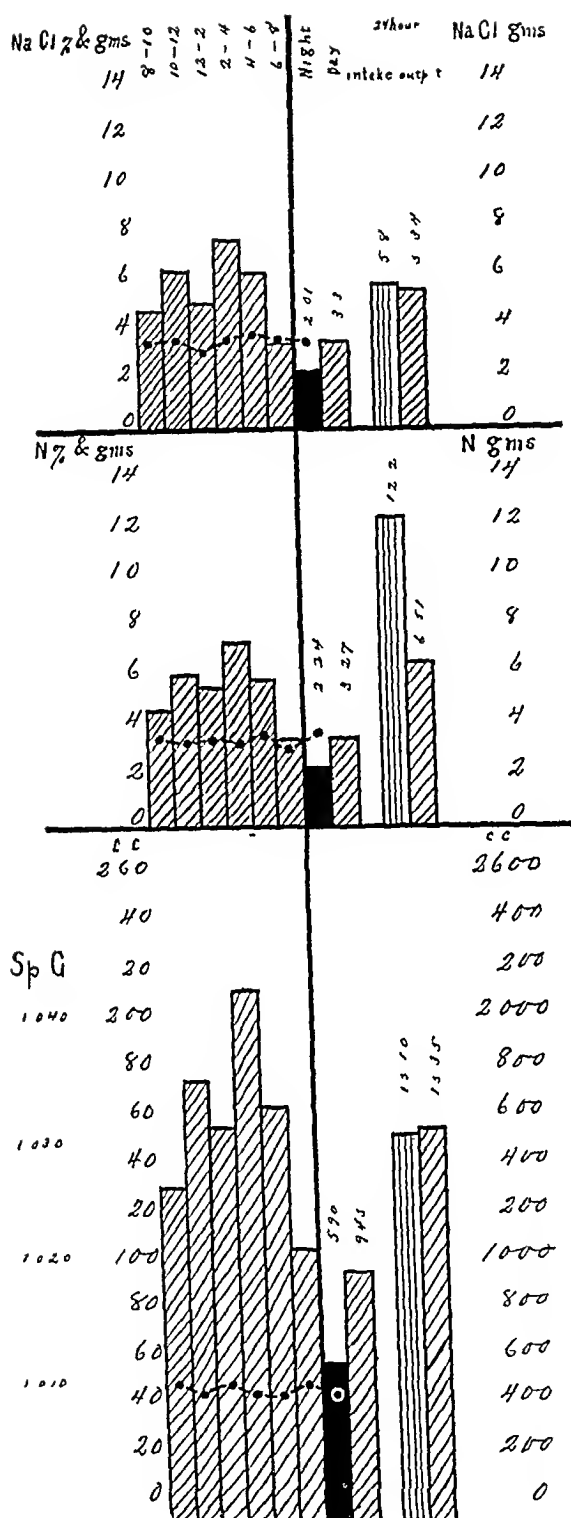


Chart 7

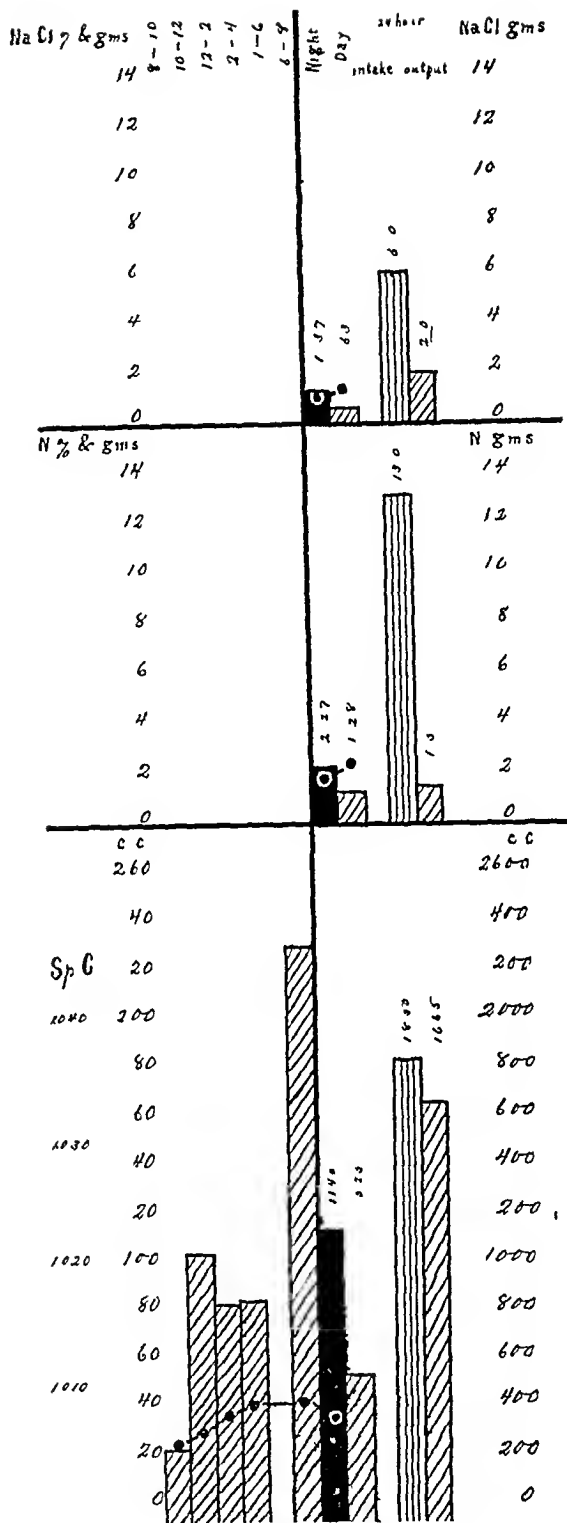


Chart 8

Chart 7—Advanced hypertensive nephritis (Systolic blood pressure in the neighborhood of 200. Albumin to 3 gm per liter, few granular and hyaline casts, albuminuric retinitis) Nephritic test meal shows markedly fixed specific gravity at the level of about 1.010 and marked fixation of the percentage quantities of salt and nitrogen. This test was repeated on two subsequent occasions and exactly the same figures obtained. There is evidently a retention of salt and nitrogen, low specific gravity and a low concentration of nitrogen at night with only slight nocturnal polyuria.

Chart 8—Extreme hypertensive nephritis (Systolic blood pressure, 200-235. Urine contains trace of albumin and a few granular casts) Nephritic test meal accentuates all the conditions found in Chart 7 to an extreme degree.

prostate, the subsidence of a pyelitis, the cure of a severe anemia, may be followed by great functional improvement, while a similar test meal picture in chronic nephritis or polycystic kidney would indicate a speedy fatal termination

Renal Congestion (Myocardial Insufficiency)—With extreme acute myocardial decompensation very characteristic results are obtained with the test meal (Table 22, Chart 13)

1 Specific gravity markedly fixed at the level of about 1 020

2 A diminished output of salt The low percentage figures for sodium chlorid are striking

3 An adequate nitrogen output The very high concentration of nitrogen is in marked contrast to that of the salt

4 An oliguria

5 A night urine normal in character

The oliguria, good nitrogen excretion, normal night urine and high fixed specific gravity readily distinguish this condition from the advanced cases of chronic interstitial nephritis

The same characteristics as those shown above are found in the patients with myocardial insufficiency persisting over a long period (Table 23, Chart 14) Similar results are also obtained in those cases in which insufficient heart action may be considered to be "slight," that is, when it is only manifested by dyspnea on exertion or slight cyanosis Thus, in this class of patients, since the kidney is so sensitive in its reaction to circulatory disturbances, the test meal becomes a valuable means of estimating the degree of myocardial insufficiency which may exist

TABLE 22—URINE IN EXTREME CARDIAC DECOMPRESSION

Time of Day	Urine		Sodium Chlorid		Nitrogen	
	c c	Sp Gr	Per Cent	gm	Per Cent	gm
8-10	61	1 018	0 20	0 12	1 52	0 93
10-12	52	1 020	0 24	0 12	1 83	0 95
12- 2	65	1 019	0 26	0 17	1 73	1 12
2- 4	55	1 018	0 27	0 15	1 65	0 90
4- 6	30	1 020	0 26	0 07	1 61	0 48
6- 8	35	1 021	0 40	0 14	1 80	0 63
Total day	298			0 77		5 01
Night, 8-8	275	1 021	0 31	0 85	1 85	5 07
Total 24 hours	573			1 62		10 08
Intake	570			5 00		12 00
Balance	— 3			+ 3 38		+ 1 92

Impression (the figures correspond with Chart 13) Nephritic test meal in an extreme case of cardiac decompensation Note the high concentration of nitrogen as compared to the low figures for salt There is distinct oliguria (The water output should be higher as general anasarca was present)

TABLE 23—URINE IN MARKED CARDIAC DECOMPENSATION

Time of Day	Urine cc	Sp Gr	Sodium Chloride Per Cent gm		Nitrogen Per Cent gm	
8-10	65	1 025				
10-12	53	1 024				
12- 2	51	1 024				
2- 4	49	1 025				
4- 6	37	1 024				
6- 8	57	1 021				
Total day	312		0 58	1 81	1 53	4 77
Night, 8-8	172	1 021	0 42	0 72	1 67	2 87
Total 24 hours	484			2 53		7 64
Intake	995			7 00		9 40
Balance	+ 511			+ 4 47		+ 1 76

Impression (the figures correspond with Chart 14) Nephritic test meal in an individual with marked cardiac decompensation which has persisted for some time The same results as in Table 19 may be noted

Hypertensive nephritis complicated by myocardial decompensation is a symptom complex met with so frequently that it demands attention in a study of this kind Table 24, Chart 19, shows the results of a test on a case of this sort It is very apparent that in this instance the characteristics of myocardial decompensation are more in evidence than those of hypertension or nephritis In other words, the congestion proves itself the predominating factor in influencing renal activity This is of interest in connection with von Noorden's⁴ statement of the variability of the specific gravity in chronic interstitial nephritis, in contrast with the usual conception of low, fixed specific gravity under these circumstances Low salt, contrasted with high nitrogen concentration and a rather high specific gravity in the urine of patients with a systolic blood pressure in the neighborhood of 200 and marked cardiac insufficiency, has been demonstrated in five cases However, instances have also been met with in which the effects of the passive congestion cannot "break through" the barrier imposed by the contracted kidney One example of this kind was found in M C, aged 50, a valet, whose systolic blood pressure varied between 235 and 180, the heart was the seat of an aortic insufficiency of luetic origin, and gave evidences of marked dilatation and hypertrophy; there were signs of extreme cardiac decompensation, marked edema, fluid in the pleural and peritoneal cavities, intense dyspnea and cyanosis The cardiac and renal diagnoses were confirmed at necropsy The immediate cause of death in this case was evidently passive congestion, resulting from weak heart action, and yet the specific gravity of the daily specimens of urine in the course of thirty-six days varied between 1 012 and 1 014, with the exception of one occasion, when it rose to 1 019

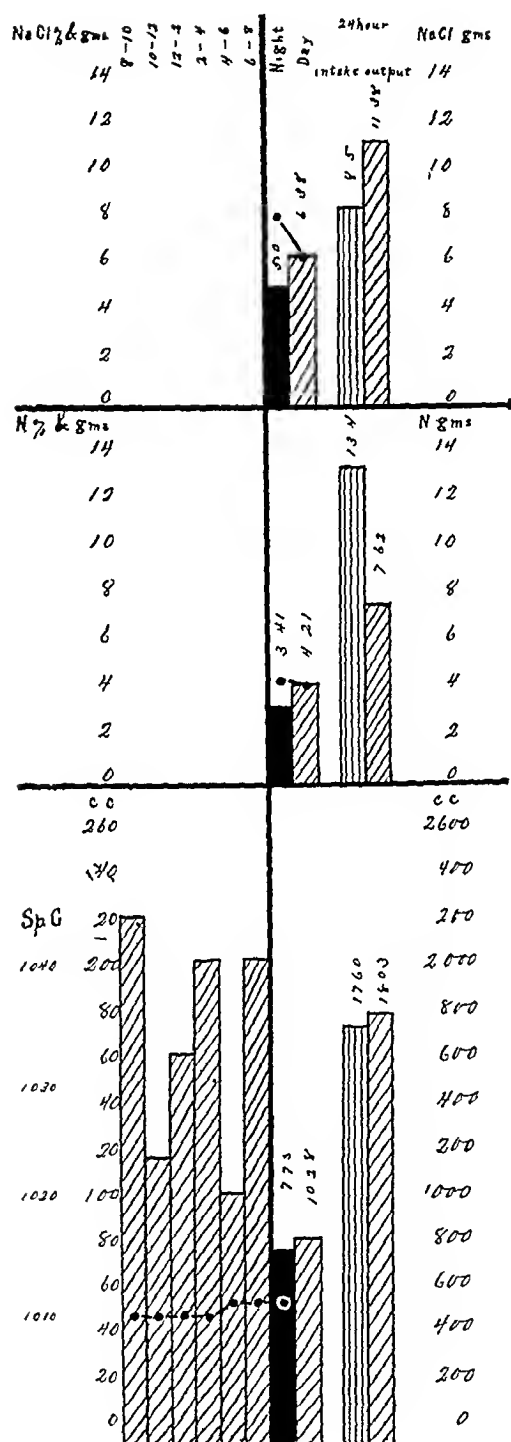


Chart 9

Chart 9—Cystitis, pyelitis, hypertrophied prostate

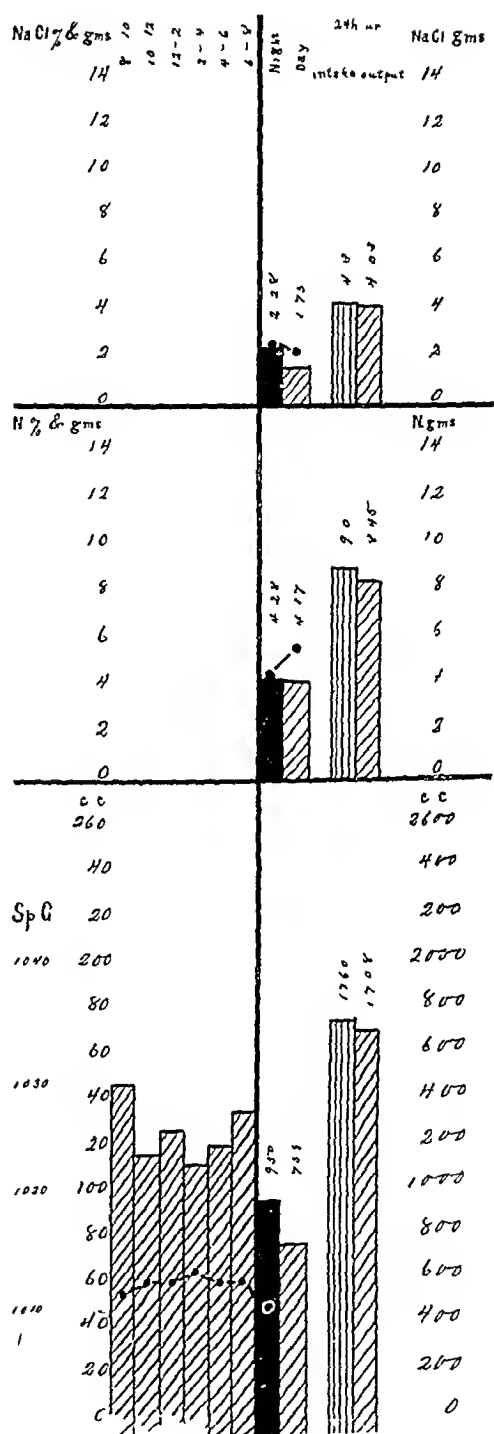


Chart 10

Chart 10—Pyelonephritis

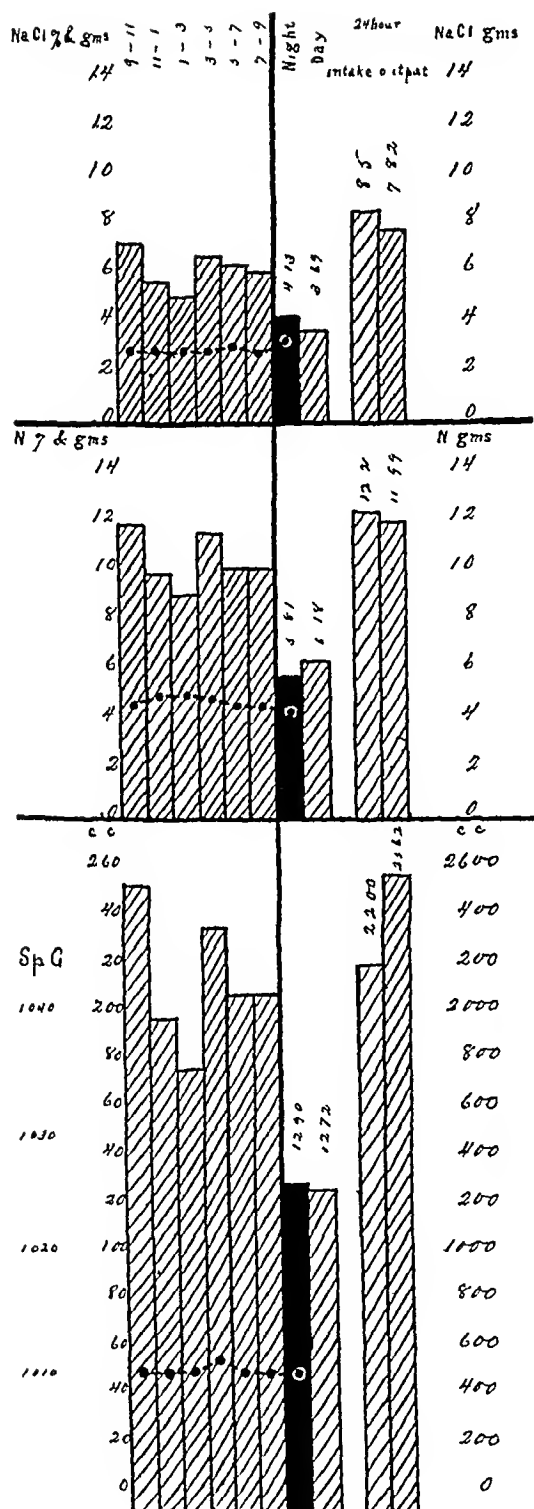


Chart 11

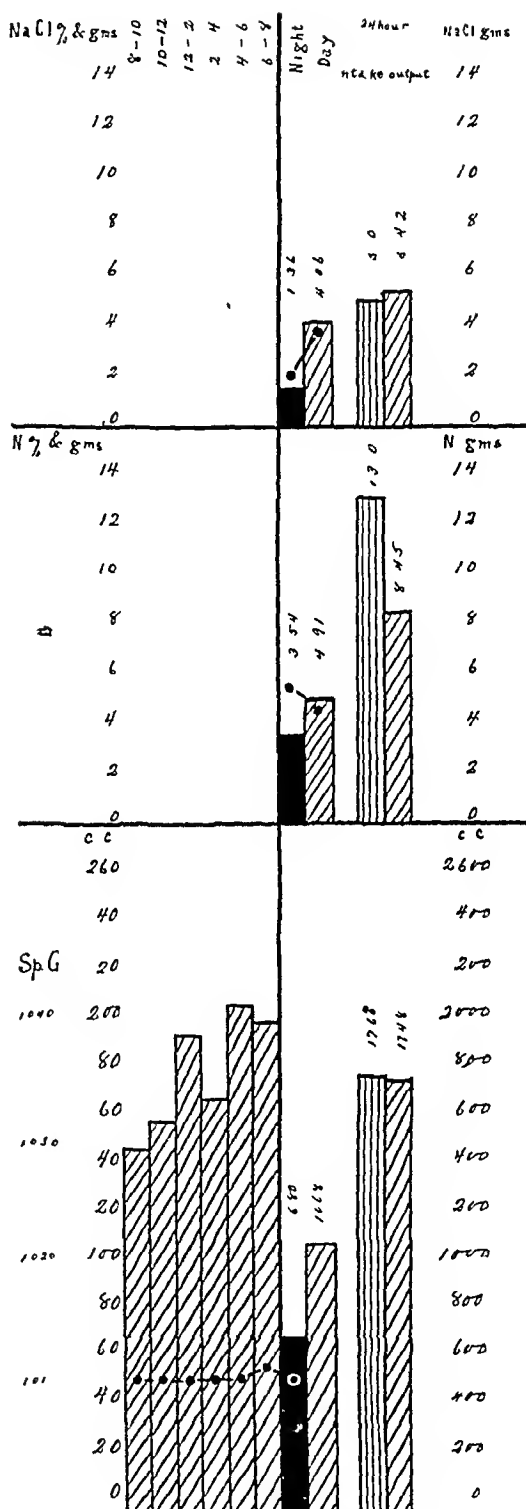


Chart 12

Chart 11—Polycystic kidney

Chart 12—Marked anemia Hb, 44 per cent, red blood cells, 2,240,000

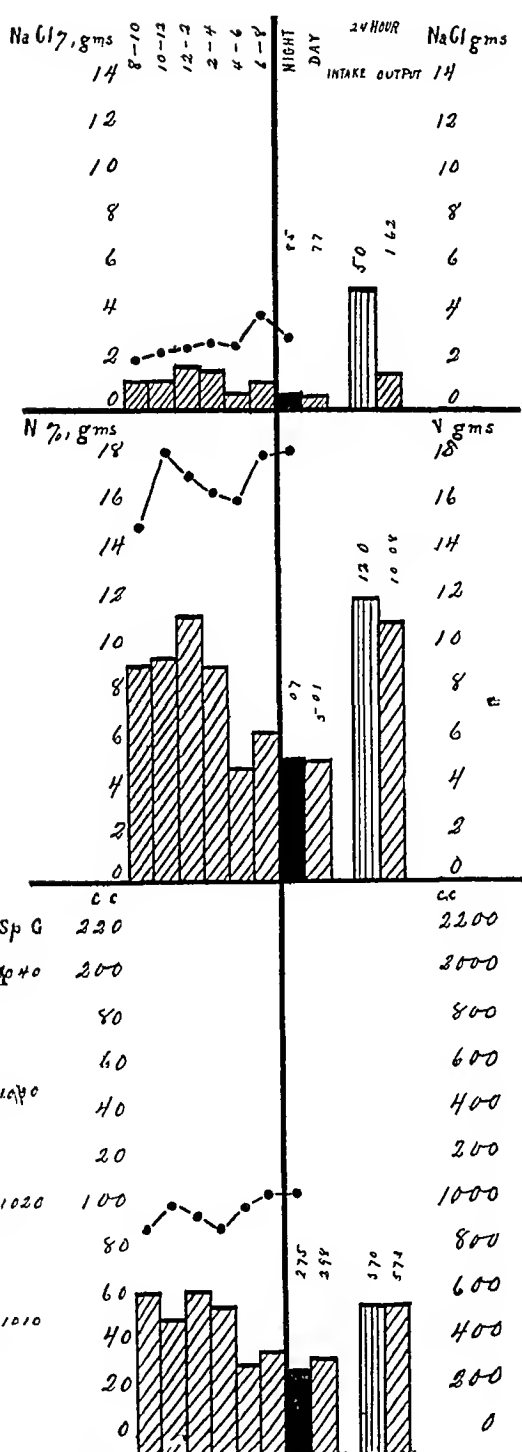


Chart 13

Chart 13—Extreme cardiac decompensation Nephritic test meal shows a low water output with a fixed specific gravity at about 1020 (The water output should be higher, as general anasarca was present) The nitrogen percentage is extremely high and nitrogen elimination is adequate There is a retention of salt and a very low concentration of salt in the urine

Chart 14—Marked cardiac decompensation Nephritic test meal shows the same changes as Chart 13, but to a less degree

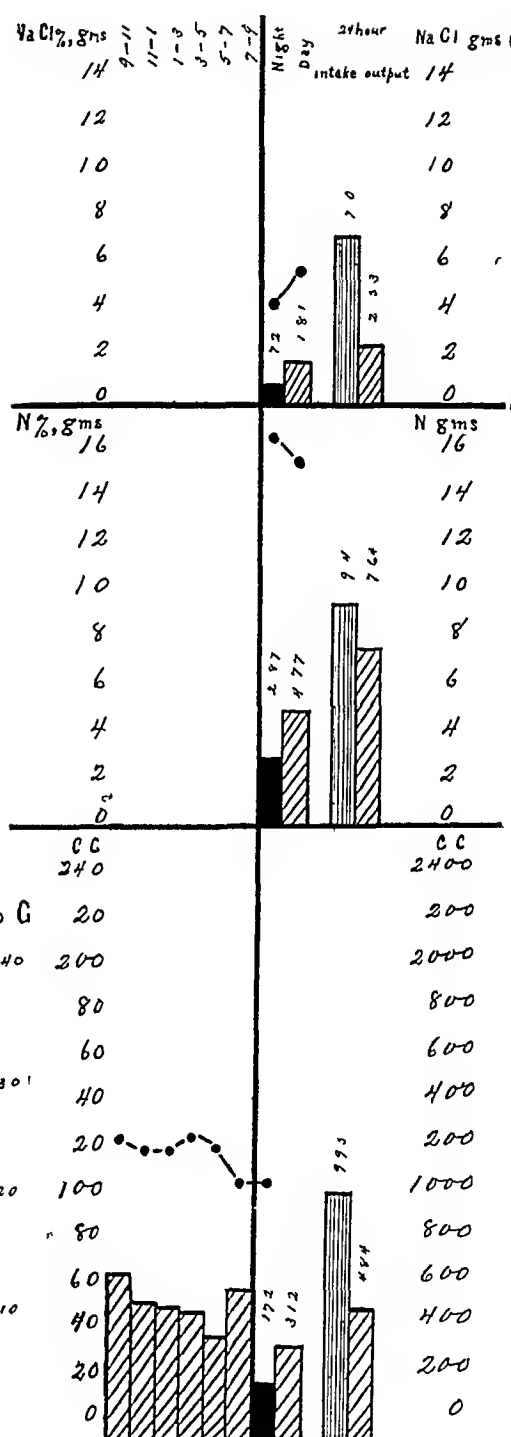


Chart 14

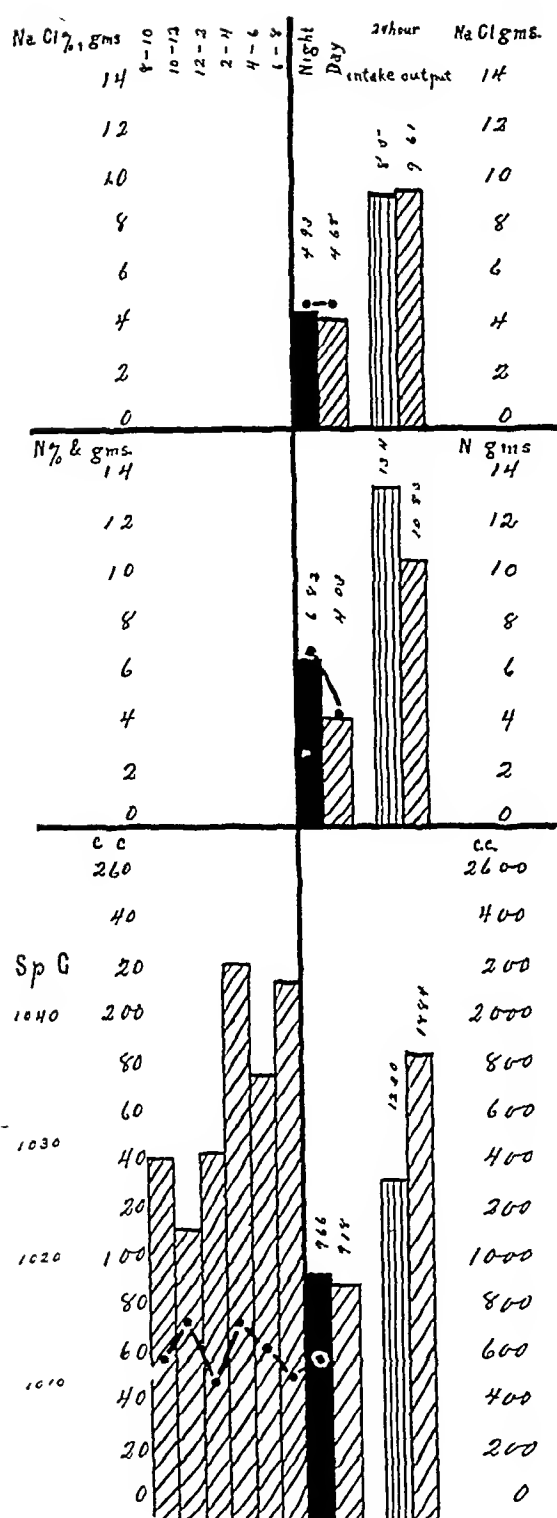


Chart 15

Chart 15—Cardiac decompensation while eliminating edematous fluid. Nephritic test meal shows a low specific gravity, nocturnal polyuria and low specific gravity at night. Salt and nitrogen eliminations are normal.

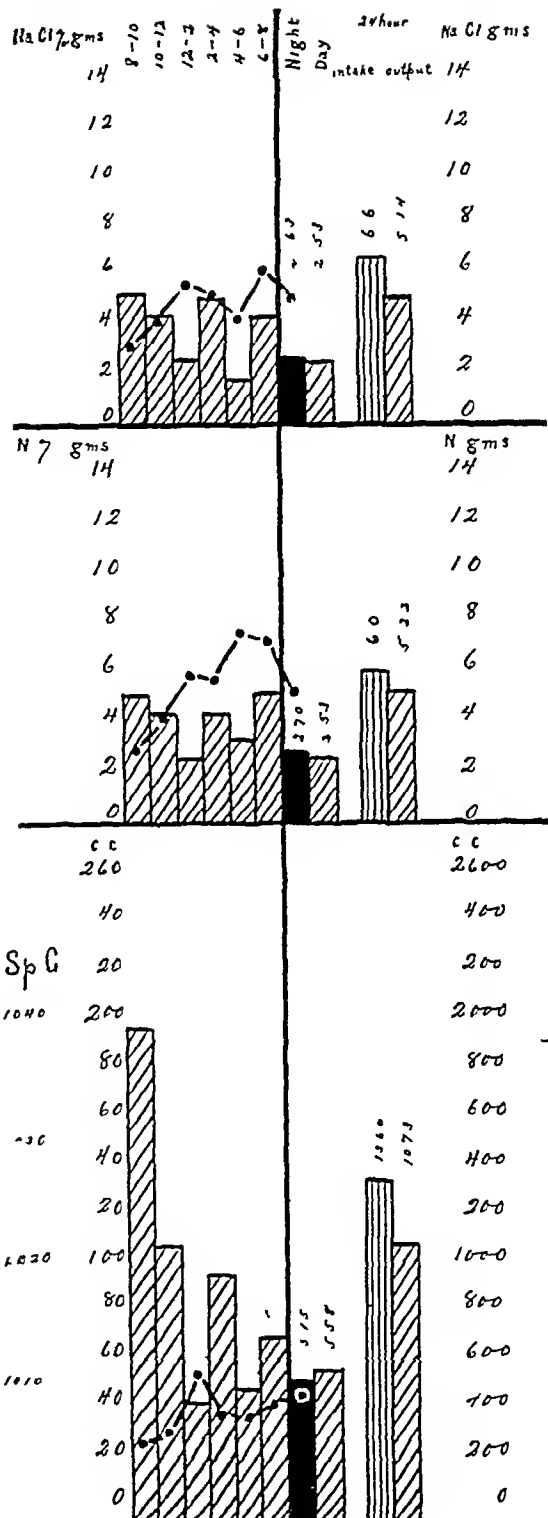


Chart 16

Chart 16—Myocardial insufficiency—after an apparently complete restoration to normal condition. Nephritic test meal shows a low, rather fixed specific gravity, a slight grade of nocturnal polyuria and a very low specific gravity in the night urine.

TABLE 24—HYPERTENSIVE NEPHRITIS COMPLICATED BY MYOCARDIAL INSUFFICIENCY

Time of Day	Urine cc	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	85	1 016	0 41	0 34	1 09	0 93
10-12	83	1 017	0 31	0 26	1 14	0 94
12- 2	100	1 017	0 41	0 41	1 04	1 04
2- 4	100	1 017	0 41	0 41	1 04	1 04
4- 6	106	1 016	0 46	0 49	0 92	0 98
6- 8	80	1 020	0 35	0 28	1 16	0 92
Total day	554			2 19		5 85
Night, 8-9	405	1 018	0 10	0 40	1 07	4 33
Total 24 hours	959			2 59		10 18
Intake	1,375			7 50		8 80
Balance	+ 416			+ 4 91		- 1 38

Impression (the figures correspond with Chart 19) Test meal curve in a case of hypertensive nephritis complicated by myocardial insufficiency. The low salt and high nitrogen elimination are characteristic of renal congestion, as is the high fixed specific gravity. It shows how the influence of renal congestion may "break through" the functional picture presented in hypertensive nephritis.

It becomes apparent that when the combination of cardiac insufficiency and hypertensive nephritis exists, the urinary symptoms of either may predominate. In the experience presented here, the characteristic urine of a passively congested kidney has been most often found. However, the number of cases studied is too small to insist on this point. Krehl,¹⁴ on the other hand, believes that under these circumstances, in spite of renal congestion, the specific gravity of the urine is low and its volume high.

After cardiac compensation has again become established in cases of uncomplicated heart disease, the urinary curve of the test meal is much changed. During the period of elimination of edema (Table 25, Chart 15), as might be expected from the polyuria existing at this time, the following characteristics are found:

- 1 Specific gravity low and somewhat fixed
- 2 Nitrogen elimination normal
- 3 Salt and water excretion exceed the amount ingested
- 4 The night urine is increased in amount, has a low specific gravity and low percentage of nitrogen

Subsequently, all the edematous fluid having been eliminated, the urinary function does not assume the normal type, as is usually supposed, but exhibits certain decided peculiarities (Table 26, Chart 16)

- 1 Low, moderately fixed specific gravity
- 2 Normal nitrogen and water output

¹⁴ Krehl. Die Erkrankungen d. Herzmuskels, 1913, p. 448

3 Slightly diminished salt excretion

4 The night urine may or may not be increased in quantity, its specific gravity and nitrogen concentration are low

TABLE 25—CARDIAC DECOMPENSATION RECOVERY, ELIMINATING EDEMA

Time of Day	Urine cc	Sp Gr	Sodium Chlorid Per Cent gm		Nitrogen Per Cent gm	
8-10	142	1 012				
10-12	114	1 015				
12- 2	144	1 010				
2- 4	224	1 015				
4- 6	178	1 013				
6- 8	216	1 010				
Total day	1,018		0 51	4 68	0 44	4 03
Night, 8-8	966	1 012	0 51	4 93	0 71	6 82
Total 24 hours	1,984			9 61		10 85
Intake	1,230			8 50		13 40
Balance	— 754			— 1 11		+ 2 55

Impression (the figures correspond with Chart 15) Nephritic test meal from a case of cardiac decompensation while eliminating edema fluid. Note the low and rather fixed specific gravity, the elimination of large amounts of salt and fluid and a night urine increased in quantity with a low specific gravity and a low percentage of nitrogen.

TABLE 26—FULL CARDIAC COMPENSATION FOLLOWING DECOMPENSATION

Time of Day	Urine cc	Sp Gr	Sodium Chlorid Per Cent gm		Nitrogen Per Cent gm	
8-10	198	1 005	0 27	0 54	0 27	0 53
10-12	108	1 006	0 42	0 45	0 41	0 44
12- 2	41	1 011	0 58	0 24	0 60	0 24
2- 4	95	1 009	0 54	0 51	0 59	0 43
4- 6	46	1 009	0 43	0 20	0 79	0 36
6- 8	70	1 010	0 61	0 43	0 74	0 52
Total day	558			2 37		2 52
Night, 8-8	515	1 011	0 51	2 63	0 53	2 70
Total 24 hours	1,073			5 00		5 22
Intake	1,360			6 60		6 00
Balance	+ 287			+ 1 60		+ 0 78

Impression (the figures correspond with Chart 16) Nephritic test meal from an individual with full cardiac compensation following a period of decompensation. The figures show considerable deviation from the normal low, moderately fixed specific gravity, slightly diminished salt output, nocturnal polyuria with a low specific gravity and low concentration of nitrogen.

This abnormal picture persists for a period of weeks and possibly months, and seems to be a distinct indication that damage has been caused to the kidney by passive congestion which does not disappear immediately when normal circulation is resumed. The urine passed during this period resembles that of advanced interstitial nephritis in many respects, and in observing the low specific gravity from day to day, the clinician is often puzzled in deciding whether such a nephritis really exists or not.

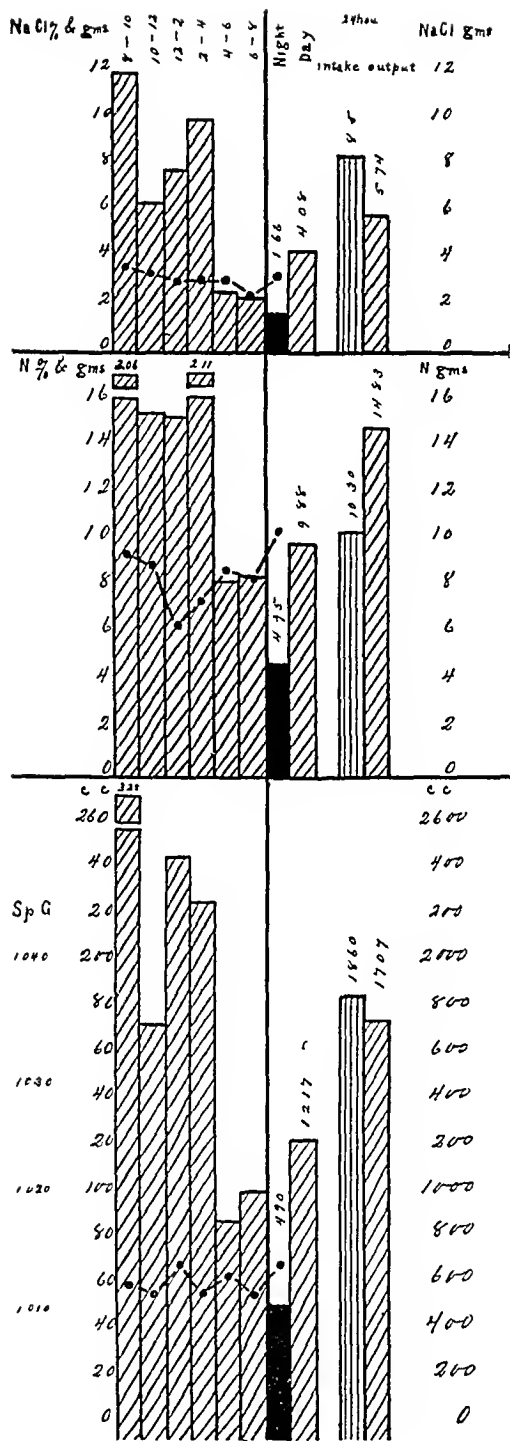


Chart 17

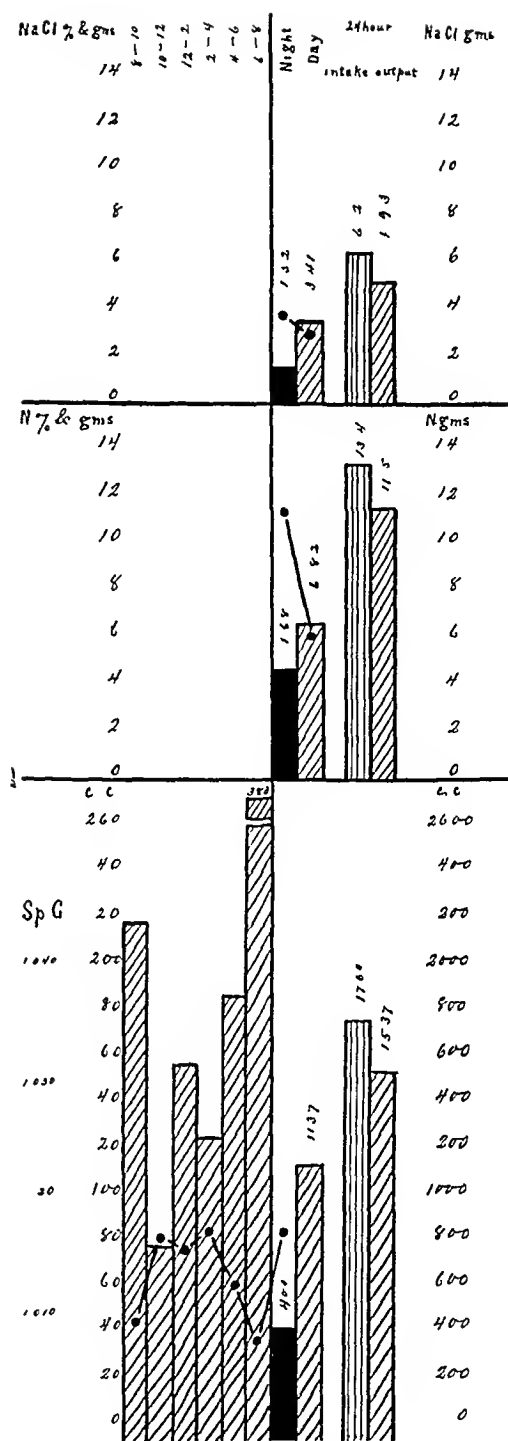


Chart 18

Chart 17—Chronic diffuse nephritis, with slight hypertension (Systolic blood pressure, 164 to 174, considerable amount of edema, urine shows a marked amount of albumin, blood, granular and hyaline casts) Nephritic test meal shows an advanced degree of involvement of renal function, very much as in Chart 7, except that the nitrogen elimination is not reduced

Chart 18—Same case as on Chart 17 after an interval of about a month, when the blood pressure had returned to normal, the red blood cells had disappeared from the urine and the edema eliminated Nephritic test meal shows a condition which approaches the normal and reflects the clinical improvement of the patient when compared with Chart 17

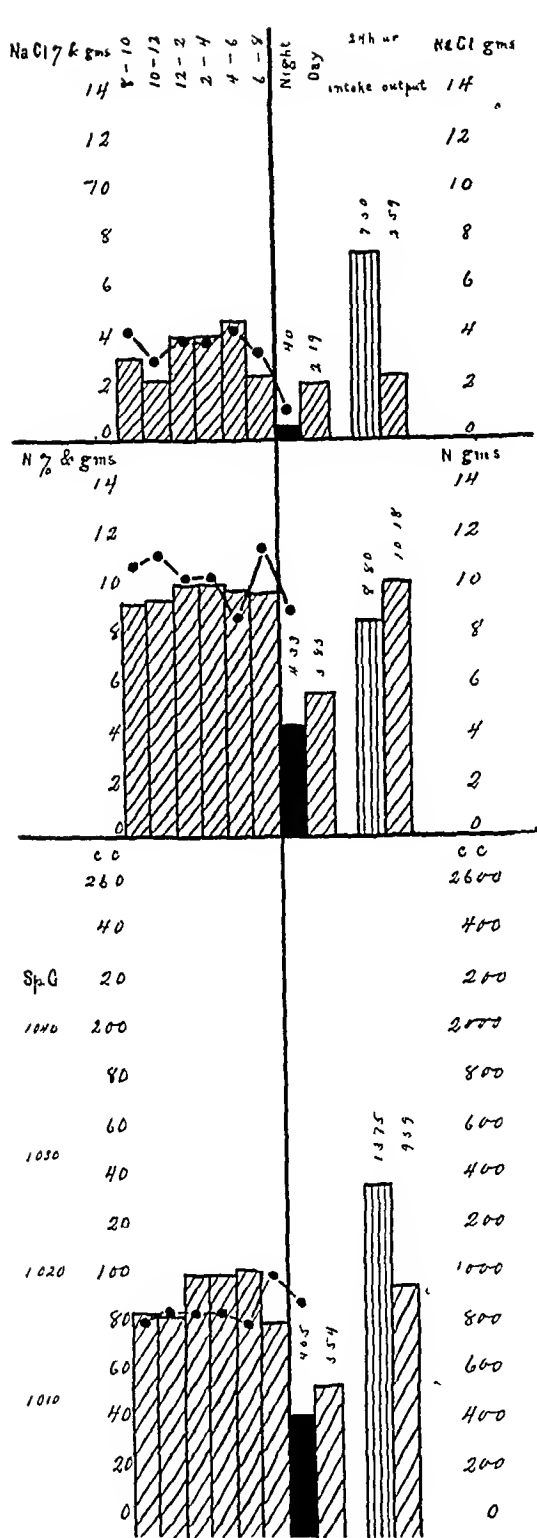


Chart 19

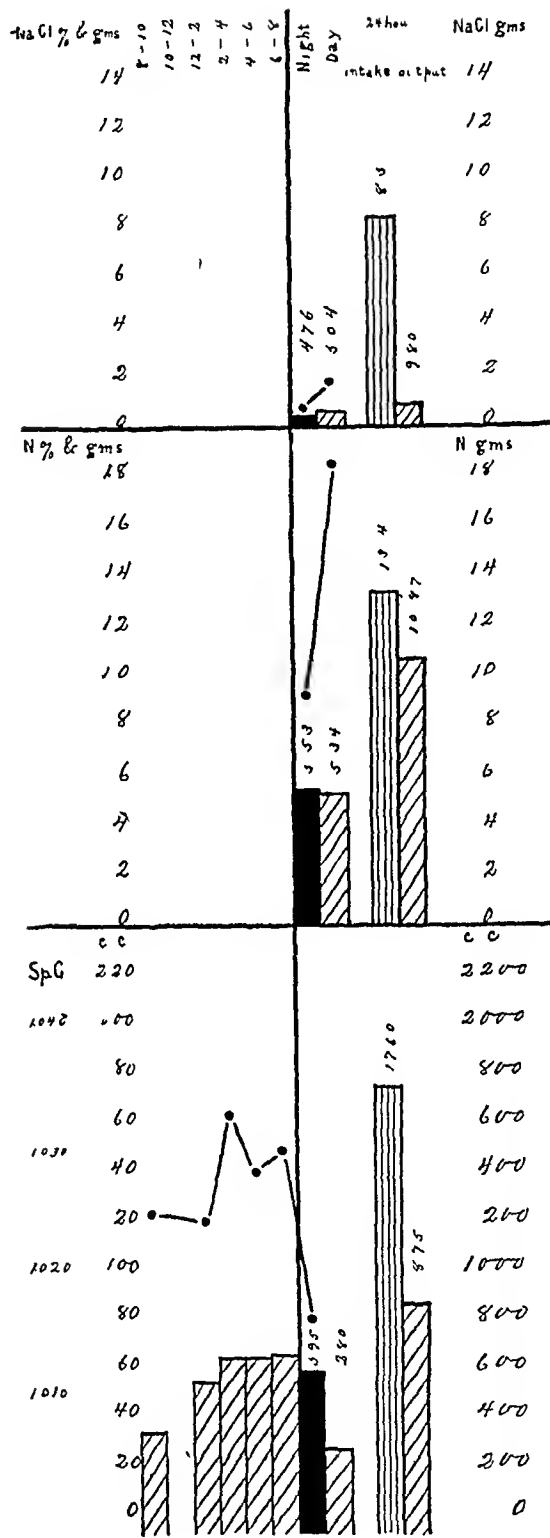


Chart 20

Chart 19—Myocardial insufficiency, combined with secondary hypertensive nephritis (Systolic blood pressure, 190 to 230. Marked albuminuria, with many granular casts) Nephritic test meal shows a result which is decidedly more characteristic of renal congestion than it is of a fairly well advanced nephritis (Compare with Charts 7 and 13)

Chart 20—Chronic diffuse nephritis Nephritic test meal shows marked salt retention, low specific gravity and low concentration of nitrogen at night, slight nocturnal polyuria and water retention

Chronic Diffuse (Parenchymatous) Nephritis—The urinary findings in nephritis of this type are as variable as the clinical symptoms. At times, clinical and functional tests are in strict accord with one another, and at others they diverge widely. During the period of edema formation, the test meal (Table 27, Chart 20) shows marked salt and water retention, a nocturnal polyuria and a good nitrogen excretion. Such urines bear a great resemblance to those seen in myocardial decompensation, and, in fact, it is at times absolutely impossible to differentiate between the two conditions from these data without having recourse to the physical signs, etc., which usually make the diagnosis an easy one.

While edema is being eliminated, the test meal again shows a marked similarity to cases of passive congestion under the same circumstances. Thus, in Table 28 (compare with Table 25, Chart 15), the amount of urine eliminated is large, the quantity of salt excreted approximates double the intake, and nocturnal polyuria is marked.

TABLE 27—CHRONIC DIFFUSE NEPHRITIS

Time of Day	Urine c c	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	32	1 025				
10-12	0					
12- 2	54	1 024				
2- 4	64	1 033				
4- 6	64	1 028				
6- 8	66	1 030				
Total day	280		0 18	0 50	1 91	5 34
Night, 8-8	595	1 016	0 08	0 48	0 93	5 53
Total 24 hours	875			0 98		10 87
Intake	1,760			8 50		13 40
Balance	+ 885			+ 7 52		+ 2 53

Impression (the figures correspond with Chart 20). Nephritic test meal in a case of chronic diffuse nephritis during the period of edema formation. The marked salt and water retention, the nocturnal polyuria and high nitrogen excretion are characteristic.

TABLE 28—CHRONIC DIFFUSE NEPHRITIS

Time of Day	Urine c c	Sp Gr	Sodium Chlorid		Nitrogen	
			Per Cent	gm	Per Cent	gm
8-10	230	1 022	1 16	2 66	1 15	2 64
10-12	130	1 025	1 08	1 40	1 42	1 85
12- 2	118	1 022	1 01	1 19	1 21	1 43
2- 4	136	1 022	1 14	1 44	1 25	1 70
4- 6	96	1 020	0 70	0 68	1 18	1 13
6- 8	108	1 014	0 80	0 87	0 89	0 96
Total day	818			8 24		9 71
Night, 8-8	950	1 014	0 78	7 61	0 73	7 14
Total 24 hours	1,768			15 85		16 85
Intake	1,760			8 50		13 40
Balance	— 8			— 7 35		— 3 45

Impression Results of the nephritic test meal in a case of chronic diffuse nephritis, while eliminating edema Note the large amounts of fluid, salt and nitrogen excreted

TABLE 29—CHRONIC DIFFUSE NEPHRITIS

Time of Day	Urine	Sp Gr	Sodium Chlorid		Nitrogen	
	c c		Per Cent	gm	Per Cent	gm
8-10	328	1 012	0 36	1 18	0 93	3 06
10-12	174	1 011	0 32	0 65	0 88	1 53
12- 2	248	1 014	0 30	0 76	0 64	1 52
2- 4	279	1 011	0 32	0 98	0 76	2 11
4- 6	88	1 013	0 32	0 28	0 92	0 81
6- 8	100	1 011	0 23	0 23	0 85	0 85
Total day	1,217			4 08		9 88
Night, 8-8	490	1 014	0 34	1 66	1 01	4 95
Total 24 hours	1,707			5 74		14 83
Intake	1,860			8 50		10 30
Balance	+ 153			+ 2 76		- 4 53

Impression (the figures correspond with Chart 17) Nephritic test meal in a case of chronic diffuse nephritis A marked involvement of renal function is evident from the low fixed specific gravity

TABLE 30

Time of Day	Urine	Sp Gr	Sodium Chlorid		Nitrogen	
	c c		Per Cent	gm	Per Cent	gm
8-10	216	1 009				
10-12	75	1 016				
12- 2	156	1 015				
2- 4	124	1 017				
4- 6	186	1 012				
6- 8	380	1 007				
Total day	1,137		0 30	3 41	0 60	6 82
Night, 8-8	400	1 017	0 38	1 52	1 17	4 68
Total 24 hours	1,537		/	4 93		11 50
Intake	1,760			6 20		13 40
Balance	+ 223			+ 1 27		+ 1 90

Impression (the figures correspond with Chart 18) Nephritic test meal from the same case as in Table 29 This test was performed about one month later and the marked clinical improvement is reflected in the result which approaches the normal very closely

An advanced degree of involvement of renal function is seen in Table 29, Chart 17 This is indicated by the low, fixed specific gravity during the night and day time After rest in bed and other therapeutic measures, the clinical aspect of this case had improved markedly, and in studying Table 30, Chart 18, it is seen that this improvement is reflected in a test meal which approximates the normal The ability of the patient to excrete salt is not well brought out in these tests In the first, there was salt retention, in the second, there was not This would have been proved had all the salt offered been taken, since in the early observations recorded it was shown that during the

first period the salt excretion represented the maximum effort of the kidney in this direction, even when more salt was added to the diet, while in the second it did not. Such pitfalls as these must be considered in the interpretation of the nephritic test meals, but with a little care they may usually be avoided.

One of the most interesting results obtained in this work has been the occasional occurrence of cases showing many of the symptoms of nephritis and little or no change from the normal response to the test meal. (The converse was noted in the cases mentioned under nocturnal polyuria.) The following was an instance of this kind.

J. C. (Medical No. 33921), a salesman, aged 47, comes to the hospital complaining of headache, the systolic blood pressure varies between 185 and 200 mm of mercury, there is considerable cardiac hypertrophy, the apex impulse being in the sixth intercostal space, 13 cm to the left of the median line, otherwise, the heart shows no abnormalities, the urine contains a trace of albumin and a few hyaline and granular casts. The test meal (Table 31) shows no abnormalities of note. This indicates that the constitutional symptoms of the nephritic complex are well advanced, but that the kidney, so far as its function is concerned, is scarcely affected. Such facts are not only of interest from the pathological point of view, but also of extreme importance in prescribing proper dietary and other therapeutic measures.

TABLE 31—NORMAL TEST MEAL CURVE IN MARKED HYPERTENSIVE NEPHRITIS

Time of Day	Urine		Sodium Chloride		Nitrogen	
	cc	Sp. Gr.	Per Cent	gm	Per Cent	gm
8-10	220	1.017				
10-12	170	1.016				
12-2	154	1.020				
2-4	182	1.018				
4-6	106	1.019				
6-8	34	1.025				
Total day	866		0.50	4.33	0.66	5.72
Night, 8-8	283	1.028	0.48	1.41	1.04	3.05
Total 24 hours	1,159			5.74		8.77
Intake	1,350			8.50		9.80
Balance	+191			+2.76		+1.03

Impression. An approximately normal test meal curve in a case of marked hypertensive nephritis. It shows how, in isolated instances, renal function may be normal in spite of extensive lesions characteristic of interstitial nephritis.

SUMMARY

The nephritic test meal, as suggested by Hedinger and Schlayer, and elaborated in this paper, has not only proved itself to be an admirable test for renal function, but also in many cases has been of great value in diagnosing cardiac, renal and other conditions. Much pleasure and profit may be derived from a study of diseases of the kidney from this point of view, since it forms a basis for a rational therapy and a stimulus towards keener clinical observation.

The test is a qualitative one of the mode of urinary function as measured by the specific gravity, salt, nitrogen and water excretion in two-hourly periods during the day, and for a twelve-hour period at night. The normal individual yields specimens with specific gravity figures which vary ten points or more from the highest to the lowest, a night urine high in specific gravity, 1.018 or more, high in its percentage of nitrogen—above 1 per cent—and small in amount—400 c c or less. The quantities of water, salt and nitrogen excreted approximate the intake. When kidney function becomes involved, the first signs are usually demonstrated in the night urine, the quantity becomes increased, the specific gravity and the nitrogen concentration are lowered. One or all of these changes from the normal may occur. In severe cases of chronic nephritis, an advanced degree of functional inadequacy of the kidney is indicated by a markedly fixed and low specific gravity, a diminished output of both salt and nitrogen, a tendency to total polyuria and a night urine showing an increased volume, low specific gravity and low concentration of nitrogen. Such functional pictures, however, are not confined to nephritis. They are found regularly in many other conditions: pyelitis, cystitis, hypertrophied prostate, marked anemia, pyelonephritis, polycystic kidney, and diabetes insipidus. The cause of diminished renal function, it is clear, must be sought for in many directions—the urinary passages, the blood or the kidney itself. Prognosis and therapy will depend largely on the cause of the fundamental impairment and not on its degree. A divergence between the degree of functional renal involvement and the intensity of the signs and symptoms of nephritis is frequently found, and accentuates the lack of parallelism that there may be between functional and anatomical lesion.

In chronic diffuse (parenchymatous) nephritis, the condition of renal function is characterized by its variability. In these instances, the results of the test meal have proved to be extremely valuable in giving an idea of the status of salt, nitrogen and water excretion, besides the picture of renal efficiency as a whole. The findings in myocardial insufficiency vary according to the activity of the heart. Distinct differences are found with myocardial decompensation and the accumulation of edema, the period of eliminating edema, and subsequently, when cardiac compensation is again fully established, it requires some time before the kidney resumes its normal activity. This intervening period is indicated by a tendency to a low, fixed specific gravity and a nocturnal polyuria. During the period of full

myocardial decompensation the results of kidney activity are very characteristic, the specific gravity is markedly fixed at the level of about 1 020, the salt output is diminished, that of nitrogen is high, in marked contrast to the salt, and there is oliguria. When chronic nephritis and cardiac decompensation coexist, as they so often do in hypertensive nephritis, the urine may exhibit the characteristics due to either lesion. The determining factor is probably to be found in the chronic nephritis which may or may not be so far advanced as to present an unchanging barrier to the influence of renal congestion.

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THE DIFFERENTIATION OF CEREBRAL AND CARDIAC TYPES OF HYPERARTERIAL TENSION IN VASCULAR DISEASE^{*}

A CLINICAL STUDY

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THE PHYSICAL CONCEPTION OF BLOOD PRESSURE

It is not sufficiently recognized, I believe, that the measurement of systolic pressure alone gives but incomplete evidence of the state of circulatory tension. Other data seem essential to an understanding of the condition, such as the constant or diastolic pressure existing between systoles and the actual head, or pulse pressure, forcing the blood column toward the periphery.

In a previous article¹ I have endeavored to establish a conception of the subject from the standpoint of dynamics and statics. In this conception the diastolic pressure represents potential energy, since the blood column exerts energy of position and not motion during diastole. During systole, when the intraventricular pressure equals or slightly exceeds the diastolic pressure in the aorta, the aortic valves open. The pressure of a given volume of blood leaving the left ventricle must, however, be considerably in excess of the diastolic pressure in order to force the blood toward the periphery. Therefore when systole occurs, the pressure exerted by the left ventricle, in order to force a volume of blood into already filled vessels, must be in excess of the pressure existing in those vessels. The transfer of energy, producing motion of the blood column, through systole of the left ventricle, must therefore be in the form of kinetic energy, which is the energy of motion. The excess of kinetic energy, as manifested by the systolic pressure over the potential energy manifested by the diastolic pressure, represents the pulse pressure or the head of pressure useful to the movement of the blood column.

It thus appears that the study of blood pressure in a given patient becomes a problem in dynamics and statics. The systolic pressure is a variable force, since it depends on the amount of kinetic energy expended for circulatory requirements at a given time. The diastolic pressure represents the less variable or constant force, its variability depending, with a given volume of blood, on the degree of contraction

^{*} Submitted for publication June 23, 1915

¹ Stone, W J Jour Am Med Assn, 1913, 1x1, 1256

and elasticity of the arterial walls. It is the sum of the diastolic and pulse pressures which make up what has been recognized clinically as the systolic pressure.

In the beginning of sphygmomanometry, attention was largely directed to the measurement of the systolic pressure, a condition of affairs which largely obtains today after more than a decade of experience. The belief may be expressed that the entire conception of blood pressure will undergo a change when it is generally understood that the diastolic is as important as the systolic pressure in an understanding of circulatory tension. If this is important from the diagnostic standpoint, it is quite as important from the prognostic point of view. A large majority of patients with hypertension fall into either the *cerebral* or the *cardiac* group. It therefore becomes a matter of importance to determine, so far as possible, in which group a patient belongs, since advice and treatment appropriate to postpone the dangers of the one might not be appropriate to postpone the dangers of the other condition.

THE AUSCULTATORY METHOD

Both pressures are most accurately taken by auscultation, with a stethoscope of the disk type, over the brachial artery on the inner aspect of the arm below the compressing arm band. Korotkoff² first described this method in 1905. In applying this method, compression is made in the arm band to a point above which all sound is heard in the artery. The air pressure is then gently released and as the pressure falls, the point at which the first sound is heard, is taken as the systolic pressure. A series of similar clear sounds are then heard (the first phase) which are soon replaced by a series of murmurs (the second phase). The murmurs are then replaced by a second series of clear sounds (the third phase). These clear tones are shortly replaced by dull tones (the fourth phase). Korotkoff believed that the diastolic pressure corresponded to the dull tone following the third phase. Ettinger³ expressed the same belief in 1907. Lang and Manswetona in 1908⁴ and Warfield in 1912⁵ have also expressed the belief, founded on experimental evidence, that the point of transition from clear to dull tones following the third phase, i. e., the fourth phase, accurately corresponded to the diastolic pressure. This has been corroborated by Taussig and Cook.⁶

2 Korotkoff. *Mitt d k mil med Akad zu St Petersburg*, 1905, xi, 365

3 Ettinger. *Wien klin Wchnschr*, 1907, xx, 992

4 Lang and Manswetona. *Deutsch Arch f klin Med*, 1908, xciv, 441

5 Warfield, L. M. *THE ARCHIVES INT MED*, 1912, x, 258

6 Taussig and Cook. *THE ARCHIVES INT MED*, 1913, xi, 542

7 Hooker and Southworth. *THE ARCHIVES INT MED*, 1914, xiii, 384

Latterly, Hooker and Southworth,⁷ using the Erlanger instrument in combination with the method of Einthoven and Geluk for recording brachial sounds, have expressed the opinion that for clinical purposes the cessation of sounds in the artery (the fifth phase) corresponds with the diastolic pressure. This point has been on the average from 2 to 4 mm lower than the fourth phase in my series of cases. I have preferred to follow in this series of cases the opinion of Warfield, Taussig and Cook, and Ettinger, in whose experimental work there seemed but little chance for error. I am inclined, however, to believe, with further experience, that in perhaps the majority of decompensated cardiac lesions the transition from the third to the fourth phase is exceedingly difficult to determine. In such instances I have taken as the diastolic pressure a reading from 2 to 4 mm above the point at which the pulse sound disappeared. It would undoubtedly simplify the procedure if the point of disappearance of pulse sound was taken as the diastolic pressure. Further experience will probably show the wisdom of adopting this point, since for all practical accuracy it answers the purpose. The systolic pressure by the auscultatory method is about 5 mm higher than by palpation, but since the former method is so much more accurate in the determination of both systolic and diastolic pressures, it should entirely supplant the latter more commonly used method.

THE HEART FORCE OR LOAD

From the clinical standpoint there can be no doubt that some means of estimating cardiac work as a circulatory force founded on pressure variations would be desirable. Strassburger⁸ first attempted in 1905 to obtain a blood pressure quotient by dividing the pulse pressure by the systolic pressure, or $P P / S P$.

Tigerstedt⁹ has also suggested this formula for determining the efficiency of the heart as a pump. The velocity of the arterial stream divided by the work of the heart gives, according to him, the efficiency of the heart as a pump. His formula is expressed as follows:

$$\frac{\text{Pulse pressure} \times \text{pulse rate} = \text{velocity}}{\text{Systolic pressure} \times \text{pulse rate} = \text{work}} = \text{Heart efficiency}$$

This is equivalent to $\frac{\text{Pulse pressure}}{\text{Systolic pressure}}$

It has been shown by many writers that either the pulse pressure multiplied by pulse rate, or the systolic pressure multiplied by pulse

⁸ Strassburger. Quoted by Barach and Marks, *THE ARCHIVES INT MED*, 1914, *LIII*, 648.

⁹ Tigerstedt. Quoted by Hirschfelder, *Diseases of the Heart and Aorta*, 1910, p 26.

rate, does not give an adequate idea of the volume output of blood from the heart. Nor is there any reason for believing that the velocity of stream divided by cardiac work, as expressed in this formula, measures heart efficiency. As mentioned below, in circulatory shock *the heart rate increases out of all proportion to the full pulse pressure*, owing to the central vasomotor influence, and the heart may be doing greatly increased work with lessened output owing to stasis in the splanchnic area. The cardiac efficiency is therefore impaired while its work is increased.

In addition, this formula appears to me objectionable for the following reasons. When the intraventricular pressure rises in systole the aortic valves do not open until the pressure equals the diastolic pressure in the aorta. The ventricular pressure, up to this point, does not avail the circulation anything at all, it being the force or pulse pressure exerted by the myocardial contraction in excess of the diastolic pressure which moves the blood column. The ratio of this pressure to the diastolic pressure should therefore be taken as the measure of work done by the myocardium in moving the column of blood.

In a study¹ of 170 patients reported in 1913 it was found that in 75 normals of various ages the average diastolic pressure was 80 mm, and that the pulse pressure was an additional 40 mm, making the systolic pressure 120 mm. The normal pulse pressure or force required to effect mass movement of blood was therefore 40/80 or 50 per cent more than the pressure required to open the aortic valves, that is, 50 per cent more pressure or force was required than the diastolic pressure. This represented a ratio or heart load which may be expressed as follows, *pulse pressure divided by diastolic pressure* or $P/P/D/P$. A load of 50 per cent was considered to be the approximate normal, which represented the fact that a pressure 50 per cent in excess of the diastolic pressure was necessary to effect movement of blood toward the periphery. The ratio may vary within normal limits between 40 and 60 per cent. During the past year about 200 normal individuals have been examined and the above ratio between pulse pressure and diastolic pressure has been found to hold true in fully 90 per cent of the cases.

I am aware that such, or any ratio, is open to certain objections, for by any method of clinical estimation of pressure in the brachial artery, it is difficult to say with certainty what conditions may exist in the remainder of the circulatory tree. In fact, it is entirely conceivable that with normal pressures in the brachial, stasis may be present in the splanchnic vessels to so marked a degree as seriously to lower the diastolic pressure without seriously affecting the systolic

pressure, although seriously affecting the output of blood moved by the heart contraction "The cardiac output is entirely dependent on the venous pressure," as Crile has stated. From the cardiac standpoint we are not so much concerned with the output of blood moved by the cardiac muscle as with cardiac work performed, which is an entirely different matter. Increased work does not necessarily mean increased output of blood moved, nor does decreased work necessarily mean decreased output. The heart may be pumping into more or less empty vessels in shock due to venous stasis in the splanchnic area and be doing greatly increased work, with corresponding increase in the pulse pressure, but with lessened output of blood from the left ventricle, for with lowered venous pressure on the right side of the heart, the output of blood would, of course, be lowered on the left side.

Since shock may be considered to result in venous splanchnic stasis, the diastolic pressure is decreased, but the force used causing pulse pressure is increased, a fact in accord with the observation of Hurthle "that with a decreased peripheral resistance there is an increase in the pulse pressure." The heart is then doing increased work, but with lessened output. This is shown in the following history. In a patient with a flank stab wound lacerating the kidney cortex, with severe retroperitoneal hemorrhage and peritonitis from puncture of the colon, the systolic pressure was 98, the diastolic 55, and the pulse pressure 43, the heart load ratio was 78 per cent during the hemorrhage. After drainage of the abdomen and enteroclysis, the diastolic fell to 38 while the pulse pressure was increased to 54 (systolic 92), the heart load ratio was 142 per cent. Shortly before death from peritonitis and acute heart failure, the diastolic fell still further to 35 and the pulse pressure was increased to 75 (systolic 110), the heart load was 214 per cent. Such was the condition in an individual with a strongly acting heart.

On the contrary, with a weak myocardium exhausted by some acute illness, the pulse pressure, as well as the heart load ratio, that is, the force available to the movement of blood, is usually low, for example

1 G M, aged 37, streptococcus septicemia, with endocarditis, all valves apparently involved, pulse rate 120 to 140, subnormal temperature for two weeks before death. The systolic pressure varied from 85 to 100, the diastolic from 70 to 75, and the pulse pressure from 10 to 25. The average pulse pressure for three days before death was 20. The average heart load for this period was 23 per cent.

2 H B, aged 54, abscess and gangrene of lung following pneumonia. The systolic pressure was 105, the diastolic 85 and pulse pressure 20. The heart load was 24 per cent eight hours before death.

3 C D, aged 24, postdiphtheritic pharyngeal paralysis, vagus paralysis (?) Pulse at wrist 36, over precordia 120, systolic pressure 90, diastolic 70, pulse pressure 20, the heart load was 28 per cent twelve hours before death.

4 Mrs R A, aged 33, probable gastric ulcer, starvation and nephritis. The systolic pressure was 115, the diastolic 100, pulse pressure 15, the heart load was 15 per cent. An unfavorable surgical prognosis was given and the patient died two weeks later from inanition.

5 Mrs P L, aged 32, acute miliary tuberculosis with intestinal perforation, showed a systolic pressure of 120, diastolic 105, and pulse pressure of 15 twelve hours after the perforation. The heart load ratio was 14 per cent. Fourteen hours later the systolic pressure was 130, the diastolic 110, the pulse pressure 20, and the heart load 18 per cent. Eight hours later, with advancing general peritonitis, the systolic pressure was 145, the diastolic 110, the pulse pressure 35, and the heart load 32 per cent. Sixteen hours later (four hours before death) the systolic pressure was 98, the diastolic 85, the pulse pressure 13, and the heart load 15 per cent.

Barach and Marks¹⁰ have recently criticized this method of estimating the percentage of cardiac force expended useful to the circulation, and while they concede that the greater number of normal cases do show the 50 per cent ratio between the pulse pressure and diastolic pressure, they believe that there is a wide range below and above this mark in normal individuals. While such a condition may have existed in their series of young individuals susceptible to psychic influences (402 out of 552 patients were between the ages of 17 and 21 years) it should not invalidate the conclusion that an average working basis for normals can with advantage be compared with the conditions found to exist generally in pathologic circulatory conditions.

I now wish to direct attention to certain groups comprising the last 75 patients with circulatory disturbance whom I have examined. For convenience these patients have been classified as follows:

- 1 Hypertension (cerebral group).
- 2 Hypertension (cardiac group).
- 3 Myocardial and valvular lesions with increased heart-load ratio.
- 4 Myocardial and valvular lesions with decreased heart-load ratio.

HYPERTENSION (CEREBRAL GROUP)

In this group of 27 patients the average systolic pressure was 202, the diastolic pressure 134, and the pulse pressure 68. The heart-load was 51 per cent. The distinctive feature of this series was the high diastolic pressure with a heart-load ratio within normal limits, 40 to 60 per cent. In other words, with an increase in the diastolic pressure, the heart muscle showed compensatory ability to meet the increased demands by an increase in the pulse pressure, with the result that the heart-load percentage was within normal limits while at rest. The important point in this series is the high diastolic pressure as an index of the degree of arterial hypertension. The terminal event in such cases is usually cerebral hemorrhage or cerebral thrombosis and edema. Although an increased heart-load may coexist, it usually is

¹⁰ Barach and Marks. *THE ARCHIVES INT. MED.*, 1914, *XLIII*, 648.

not the important feature barring overstrain This is shown in Case 9 of Table 1, in which the heart-load was 105/130 or 81 per cent The morning on which this observation was taken this patient had suffered a hemiplegia Her heart-load decreased under the enforced rest to normal 51 per cent a few months later, but the diastolic pressure remained high, varying from 130 to 145

Under the cerebral group are found many of those patients with high diastolic pressures and cerebral symptoms the terminal events of which have for many years been placed under the heading of uremia They are usually placed under this heading because of the history of night polyuria, with urine of low specific gravity and the temporary or constant presence of albumin with tube casts The exitus usually occurs in rapid or gradual coma under the title of uremia The symptoms in such instances are those of cerebral thrombosis and edema, and as such should be so designated There is no question that the kidneys present, in such cases, evidences of diffuse or interstitial changes and as such are seriously damaged as functioning organs, but it is comparatively rare to see such patients with chronically damaged kidneys die in anuria The point is that the essential change involves the smaller blood vessels all over the body, and that the symptoms of the terminal event concern an edema of the brain as well as the kidneys The kidney involvement is concomitant and not the essential change As Janeway¹¹ has stated, "The most prominent symptoms associated with high blood pressure are circulatory rather than renal" He states also that there has been a marked tendency to return to the view of Gull and Sutton (1872) that the disease is primarily a disease of the smaller blood vessels In fact, Richard Bright¹² in 1836, referred to some of the symptoms of nephritis as manifestations of "vascular disease," a term which may well be retained as descriptive of the symptom complex

In Janeway's series of cases death occurred in the following order of frequency

- 1 Gradual cardiac insufficiency
- 2 With uremic symptoms
- 3 Apoplexy
- 4 Some complicating acute infection
- 5 Angina pectoris
- 6 Acute edema of the lungs

It is probable that the first and sixth divisions of this group could be combined, since the symptoms of acute pulmonary edema rarely occur without evidences of myocardial exhaustion It will thus be

11 Janeway, T C THE ARCHIVES INT MED, 1913, xii, 755

12 Bright, Richard Guy's Hosp Rep, 1836, 1

No	Name	Age	S P	D P	P P	Cardiac Load Per Cent	
1	Miss E K	52	200	125	75	60	Fatigue and dyspnea on exertion, pressure in head, 11/25/13
2	" "					48	Trace albumin, 12/27/13
3	Miss I Y	42	200	135	65	60	Retinal hemorrhage, plethora, urine neg
	Miss M	25	185	115	70	60	Edema, decreased urinary output with albumin, 120 gm per liter, acute exacerbation Chronic diffuse nephritis Death one year later
4	Mrs G S	49	210	135	75	56	360 cc urine in twenty-four hours, much albumin, chronic interstitial nephritis, death in coma due to cerebral edema
5	F O	42	205	135	70	52	Angina, pressure in head, syncopal attacks, improved by venesection, urine previously contained albumin and casts, now negative
6	Dr S T	84	180	120	60	50	Cheyne-Stokes breathing intermittently, occasional extrasystole, thrombosis of ant tibial artery
7	Dr W W	39	220	160	60	37	Comatose from cerebral hemorrhage, urine solid with albumin, death one week later
8	Mrs W J	56	180	130	50	38	Fatigue on slight exertion, dizziness, death one year later with gradually falling pressure in coma, symptoms of uremia due to cerebral edema
9	Mrs H P	62	235	130	105	81	Pain in arms, dyspnea on exertion, paroxysmal vertigo, slight hemiplegia, urine negative, 12/24/13
	" "		220	145	75	51	Vertigo and mental confusion, urine negative, 9/12/14
10	Miss E B	53	190	120	70	58	History of two slight apoplectic seizures with weakness of right arm and leg, also of headaches and dizziness Urine contains much albumin, now loss of bladder and rectal control, systolic murmur over aorta, sudden death four months later
11	M G B	49	225	140	85	60	History of night polyuria Urine contains albumin and sugar, heart shows systolic murmur at apex, ringing second aortic, gallop rhythm Death seven months later, general and pulmonary edema
12	J H P	52	220	140	80	57	Headaches, mental confusion, earlier dyspnea, relieved by digitalis, 8/18/14
			210	135	75	55	Urine, albumin positive Specific gravity low, night polyuria, 9/28/14 Death in coma three months later, cerebral edema

13	P J J	54	190	140	50	35	Nocturnal headaches and polyuria, dizziness, urine contains much albumin, heart negative, except accentuated second aortic Much vertigo, 2/26/15
14	Mrs R G S	44	225 195	160 130	65 65	40 50	Vertigo on exertion, cardiac hypertrophy one inch to left, accentuated first tone at apex, urine negative
15	J W D	67	215	130	85	65	Complains of vertigo, systolic blow over aorta, urine negative
16	Miss M K	50	225	130	95	73	Vertigo, fatigue, urine negative
17	Mrs L E C	64	190	120	76	58	Syncopal attacks, angina, suffocation, systolic murmur apex, urine negative Death one year later, angina pectoris, 10/13/14
18	M L C	69	195	135	60	44	Vertigo, accentuated second aortic, irregular and intermittent pulse
19	C B	54	180	120	60	50	Much albumin and sugar in urine, polyuria (5,000 cc in twenty-four hours)
20	Gen E R K	72	200	120	80	66	Chronic nephritis, death one month later in coma with cerebral and pulmonary edema
21	P L	38	205	135	70	51	Vertigo and headache, urine contains much albumin, nocturnal polyuria
22	Mrs K	38	165	135	30	22	Acute exacerbation, chronic diffuse nephritis, blind before becoming comatose, cerebral edema, urine 1,000-1,200 cc in twenty-four hours, contains much albumin, five days before death
23	Rev E M A	51	220	130	90	69	Mental confusion, failing memory, weakness, night polyuria, low specific gravity, much albumin, many casts
24	J P	58	185	135	50	37	Dyspnea of sudden onset, edema of limbs, ascites, swollen liver, cyanosis, urine contains albumin, cardiac dilatation (?) Death one month later
25	Mrs M G	24	230	170	60	35	Evidences of nephritis for six years, facial paralysis of central origin, night polyuria, much albumin, many casts and blood cells
26	Mrs J V	60	195	150	45	30	Frequent subconjunctival and dermic hemorrhages, dyspnea on exertion, cardiac hypertrophy, systolic murmur loudest over aorta, marked accentuated second aortic, sclerosis arch aorta, myocardial fatigue Urine 1007, polyuria, albumin present
27	J H T	63	190	145	45	31	Urine negative in 1912, now complains of dyspnea due to emphysema and myocardial fatigue, indistinct heart tones, pulse rate 120 after slight exertion, urine contains much albumin

seen that the two most common causes of death in hyperarterial tension are cardiac and cerebral. For convenience the following classification may be used

Death in hypertensive vascular disease	1 Cardiac	{ 1 Myocardial exhaustion 2 Angina pectoris	{ Dilation Acute pulmonary edema
	2 Cerebral	{ 1 Thrombosis and edema associated with disturbed renal function 2 Hemorrhage	

Janeway has stated that the exact height of the blood pressure did not seem to have much bearing on life expectancy. This conclusion was based on evidence secured by systolic readings alone in probably the larger proportion of his cases. Every physician is familiar with the fact that some patients may live for many years with extremely high systolic pressures providing cardiac strain is avoided and due care is taken to secure adequate rest and proper elimination. Such a conclusion depends, however, not so much on how high the systolic pressure has become, but rather on the height of the diastolic pressure and the quality of stock in the arterial walls. Janeway's statement consequently needs modification. I am certain, speaking from the standpoint of hypertension, that an individual with a systolic pressure of 200 and a diastolic pressure of 140, is in greater danger of cerebral death than an individual with a systolic pressure of 200 and a diastolic pressure of 100. I am likewise certain that the individual with a systolic pressure of 200 and a diastolic of 90 to 100 is in greater danger of a cardiac death. It is apparently the constant high diastolic pressure rather than the intermittently high systolic pressure which predisposes to cerebral accident. If this were not true, cerebral death would occur much more frequently in the cardiac group of hypertension (see below), a condition which in my experience has rarely occurred, although the systolic pressures in many patients of the cardiac group were as high as the systolic pressures in those of the cerebral group. Records of the diastolic pressure become of importance, therefore, as an aid in prognosis and advice as to treatment.

In the cerebral hypertension group, the main symptoms were pressure in the head, vertigo, nocturnal headache, wearing off usually by noon, mental confusion, retinal and subconjunctival hemorrhages, fatigue on exertion and a history of nocturnal polyuria. Objectively, the urine may contain albumin, is of low specific gravity, the total quantity is increased, and periodically abundant casts are found. The radial and femoral arteries are rigid, the second aortic tone is ringing in character and a systolic murmur may be present at the apex, transmitted to the right toward the aorta. As before mentioned, the diastolic pressure is high, from 120 to 160, and if the individual has been

able to avoid undue exertion and has a compensating heart, the systolic pressure is high also. If cardiac dilatation has occurred, even though slight in degree, from some unusual exertion, the systolic pressure is lower, which with little change in the diastolic pressure, produces an altered ratio and a diminished heart-load percentage. This is illustrated in Case 24 of Table 1 and Case 1 of Table 4, in which cardiac deaths occurred in patients of the cerebral type. Generally, however, in the cerebral group, the death occurs from hemorrhage or with the symptoms of cerebral edema, usually designated uremia.

HYPERTENSION (CARDIAC GROUP)

Of the twenty-four patients in this group, the average systolic pressure was 180, the diastolic pressure 92, and the pulse pressure 88. The heart-load ratio was therefore increased from the normal of 50 per cent to 96 per cent. The distinctive feature of this group was the low diastolic pressure as compared with the cerebral group. Most of these patients showed arterial hardening, but the contraction of the smaller blood vessels could not have been so marked or the diastolic pressures would have been increased. Practically all showed cardiac hypertrophy at some time in compensation, which had resulted not so much because of the increased peripheral resistance, but because of sclerotic damaged valves, coronary sclerosis, or as a result of extra-cardial factors, such as dilatation of the aortic arch, liver cirrhosis, gout, syphilis or hard physical labor, calling for unusual cardiac demands.

In the cardiac hypertension group, the main subjective symptoms were fatigue on exertion and dyspnea, anginoid pains in chest, edema of extremities and palpitation. Objectively, the heart was usually hypertrophied, the rate was in a number of instances of the perpetually irregular type, or was intermittent, due to extraventricular systoles, systolic murmurs were found in a number of instances over the base or apex, transmitted toward the aorta and into the vessels of the neck, pointing to sclerosis of the aorta. The second aortic tone was usually accentuated. *The urine was negative to albumin and casts in a large majority*, but the quantity was usually diminished. None of the patients in this series showed the nocturnal polyuria or symptoms of nephritis, so common among the patients in the cerebral hypertension group. The death occurs most frequently with the symptoms of a gradually failing heart muscle. The systolic pressure remains high until the heart muscle begins to fail and then gradually falls as the muscle tone diminishes (the so called "primary high, secondary low" sequence). One frequently encounters in the literature the statement that normal pressures are found to be present shortly before death in

No	Name	Age	S P	D P	P P	Cardiac Load Per Cent	
1	Mrs S F	78	150	80	70	87	Left arm and leg weakness for three months, cerebral embolism and softening, systolic murmur over aorta transferred to neck, sclerosis of arch
2	Mrs H U	57	190	108	82	69	Dyspnea, edema of ankles for years following rheumatism, apex in anterior axillary line, acute bronchitis, rate 136, temperature 101, perpetual arrhythmia
3	Mrs N N C	70	160	70	90	128	Mitral stenosis and regurgitation moderate, periodic dyspnea, arteriosclerosis
4	I R	77	170	100	70	70	Fatigue, hypertrophy left ventricle, emphysema
5	Mrs E R K	66	185	95	90	94	Inspiratory dyspnea, anginoid pains in chest, cardiac hypertrophy
6	Mrs A W	72	205	115	90	78	Nocturnal dyspnea, fatigue on exertion, cardiac hypertrophy
7	S M H	81	170	85	85	100	Dyspnea on exertion, urine contains nucleos and sero-albumin due to catheter life, no cerebral symptoms
8	Mrs E B	77	180	90	90	100	Secondary anemia, reds 2,500,000, systolic blow over base, urine negative, precordial distress, fatty heart
9	G P	65	152	78	74	94	Fatigue on exertion, gout, sclerotic radials, intermittent pulse, hypertrophy left ventricle
10	Mrs C G	66	175	75	100	133	Dyspnea, cardiac asthma, marked irregularity due to extraventricular systoles, rate 60, 2/23/14
			185	105	80	76	Much improved under digitalis and sodium iodid, rate 84, 3/9/14
11	Mrs F W	48	160 220	60 100	100 120	166 120	Return of dyspnea, 4/26/14
12	Mrs McC	71	195	105	90	85	Sclerosis aorta, hypertrophy left ventricle, relative aortic insufficiency
			195 165 170 195	90 75 90 85	105 90 80 110	117 120 88 130	Palpitation and irregularity, dyspnea on exertion, 1/6/13
		72					Weakness and loss of weight, 6/23/13
							Weakness and loss of weight, 7/23/13
							Edema ankles, urine negative, 9/8/13
							Vertigo and dyspnea, 9/14/14

13	Mrs M S	42	160	90	70	77	Perpetual arrhythmia, rate 112-116, murmurs over all valves, anascara, sudden death two and one-half months later, 10/8/13
14	Mrs S A J	48	180	110	70	63	Obesity, fatty heart (?), systolic murmur over base and aorta, urine negative, edema of limbs to knees
15	L A	67	160	90	70	77	Moderate dyspnea, systolic murmur over apex transmitted to aorta, sclerosis of, urine negative, although albumin and sugar had previously been present Death six months later in coma, probably cerebral
16	Mrs M D	63	178	100	78	78	Dark spots before right eye, probably old retinal hemorrhage, heart negative except accentuated second aortic, urine negative
17	Miss S J	55	210	110	100	90	Occasional tachycardia alternating with bradycardia, no syncopal attacks or vertigo, accentuated second aortic, urine negative
18	Mrs S J	40	175	100	75	75	Dyspnea and cough, presystolic and systolic murmur apex, accentuated second pulmonary, edema extremities, cyanosis lips in prone position
19	C W E	62	160	110	50	45	Vertigo and headaches, urine negative, systolic murmur apex transmitted to aorta, sclerosis of, perpetual arrhythmia, rate 56
20	W M	67	170	80	90	112	Dyspnea, anginoid pains in chest and epigastrium, cough, albumin positive from stasis, death one month later, myocardial failure
21	J B	54	190	90	100	111	Mitral regurgitation, dilatation arch aorta (?), sudden death three days later
22	Miss J L	40	180	95	85	90	Paroxysmal tachycardia, heart block (?), systolic murmur apex, dyspnea
23	Mrs S S T	71	240	105	135	128	Obesity, systolic murmur base and arch aorta, edema extremities, polyuria, syncopal attacks, pulse rate 32 to 36 for three months, due to heart block
24	Mrs D A C	68	180	90	90	100	Complains of irregular heart action, palpitation and dyspnea on exertion, cardiac hypertrophy to left, systolic murmur upper aorta, accentuated second pulmonary, urine negative

such cases and that in consequence blood pressure readings give one little clue as to the sequence of circulatory changes. To this I agree to the extent that an isolated reading of pressure in a patient during his last days of illness with vascular disease can be of little value. But readings at such times when compared with earlier readings taken before the break in compensation, would much more clearly explain the sequence of events leading to the gradual or rapid fall of systolic pressure as the myocardial force diminished. The systolic pressure frequently falls from 180 or 200 to 120 or below over a period of weeks or months as the myocardial force diminishes. With the low or normal diastolic pressures found in the cardiac group this would result in a heart-load ratio within normal limits (except in aortic regurgitation). If comparative readings had been made earlier in the disease it would have been found that the heart-load ratio like the systolic pressure was increased. This is shown in the following brief history of Case 3, Table 4.

Seven months before death the patient's systolic pressure was 180, diastolic 90, pulse pressure 90, heart load 100 per cent. As the myocardial force diminished, the systolic gradually fell to 125, diastolic 90, pulse pressure 35, and the heart load was 35 per cent. The ratio improved with compensation, so that after a few weeks the load was within normal limits, 58 per cent. Gradually decompensation occurred with tachycardia, absolute arrhythmia and acidosis. The systolic pressure was 100, diastolic 80, pulse pressure 20, and heart load 25 per cent a few hours before death.

MYOCARDIAL AND VALVULAR LESIONS WITHOUT HYPERTENSION BUT WITH INCREASED HEART-LOAD PERCENTAGE

In this group there were 14 patients. The individual age was much lower than in the preceding groups. Excluding the 4 patients with aortic insufficiency, the systolic pressure averaged 112, the diastolic 60, and the pulse pressure 52. The heart-load ratio was 86 per cent, an increase above the normal of 36 per cent. The greatest increases in the heart-load percentage were in the four patients with aortic regurgitation, in which the average systolic pressure was 138, the diastolic 40, the pulse pressure 98, and the heart-load 245 per cent. In the consideration of heart-load, instances could be cited in which there existed a load of 100 per cent, that is, an overload of 50 per cent, with few subjective symptoms of myocardial incompetency. Most of these patients were able so to regulate their lives that little cardiac strain occurred. It is merely to be emphasized that when the pulse pressure persistently equals the diastolic pressure with a resulting 50 per cent *overload*, which means the expenditure of double the normal amount of kinetic energy on the part of the heart muscle, cardiac hypertrophy has occurred. The symptoms of cardiac incompetency may develop at any time of slight overstrain. Of course, the

presence of incompetent valves greatly adds to the myocardial embarrassment. This is especially true of aortic regurgitation, in which the load is greatly increased as mentioned above. This condition has long been recognized as one of the most serious of valvular lesions.

MYOCARDIAL AND VALVULAR LESIONS WITH DECREASED HEART-LOAD PERCENTAGE

In this group there were 10 patients, all of whom showed various degrees of cardiac dilatation or marked degrees of cardiac muscle weakness. In dilatation there is, as a rule, a more or less marked fall in the systolic pressure, pointing to the inability of the myocardium to furnish the requisite energy, while there is less change in the diastolic pressure. This produces a diminished pulse pressure until with marked incompetency there is little pressure in excess of that required to open the aortic valves, that is, the diastolic and systolic pressure tend to approximate each other. This is especially shown in Case 6 of Table 4. The average systolic pressure in this Group was 118, the diastolic 92, the pulse pressure 26 and the heart load 28 per cent. These cases show, I believe, such a marked reduction in the heart-load percentage because of myocardial fatigue or dilatation. The diminished heart-load corresponds to the "negative load" recently mentioned by Swan¹³.

This point has appeared to need emphasis, since it is a factor of importance not so much in the diagnosis of a marked degree of dilatation, as in those of lesser degree, in which, regardless of the skill of the physician in percussion, it is difficult, if not impossible, accurately to outline changes in the area of heart dulness.

CONCLUSIONS

From the study of these conditions, the following conclusions appear warranted.

1 The determination of systolic and diastolic pressures by the auscultatory method should supplant the palpatory method. The comparison of systolic, diastolic and pulse-pressure is of value in the clinical interpretation of circulatory changes and of more importance than the estimation of systolic pressure alone.

2 The pulse pressure measures the energy of the heart in systole in excess of the diastolic pressure. For clinical purposes it represents the load of the heart. Under normal conditions, it is approximately 50 per cent of the diastolic pressure. The heart-load may therefore be expressed by the fraction,

$$\frac{\text{Pulse Pressure}}{\text{Diastolic Pressure}} \quad \text{or} \quad \frac{P P}{D P}$$

¹³ Swan, J. M. THE ARCHIVES INT. MED., 1915, LV, 269

TABLE 3—MYOCARDIAL AND VALVULAR LESIONS WITHOUT HYPERTENSION BUT WITH INCREASED HEART LOAD RATIO

No	Name	Age	S P	D P	P P	Cardiac Load Per Cent	
1	C McC	11	130	50	80	160	Acute exacerbation of chronic endocarditis, double murmur in femoral and brachial, capillary pulse, aortic insufficiency Cyanosis with edema of limbs, extreme dyspnea, apex in left anterior axillary line, systolic and diastolic murmurs over all valve areas, capillary pulse, aortic insufficiency, 8/28/14 Ten hours before death, 8/30/14 Dyspnea, marked irregularity, rate 52, emphysema, chronic bronchitis, improved on caffeine, myodegen cordis Dyspnea and fatigue, mitral stenosis and insufficiency, marked irregularity, rate 56, irregularity increased under digitalis Fatigue on exertion and insomnia, systolic murmur over apex and loudest over aorta, transmitted to neck, slight dilatation of arch Periodic syncopal attacks with bradycardia to 28-32, positive venous pulse, relative tricuspid insufficiency, heart block
2	Mrs R G	25	138	35	103	300	
3	M R	69	145 125	35 58	110 67	314 115	
4	Miss J T	25	128	72	56	77	
5	Mrs W W	54	138	85	53	62	
6	S C	13	90	55	35	63	

7	L G V	54	90	50	40	80	Blurring vision, diarrhea and vertigo, luetic myocarditis and liver cirrhosis, one month before death
8	H L	46	125	68	57	84	Partial syncope following undue exertion, left ventricle hypertrophy, "athletic heart"
9	P M	17	95	40	55	72	Acute infection undetermined origin, hemolytic anemia, red blood cells 952,000
10	H C	18	110	60	55	83	Eventual recovery
11	R S	21	140	20	120	600	Mitral regurgitation with apparent compensation
12	M S	34	140	60	80	133	Aortic insufficiency and chronic endocarditis, diphtheroid bacillus recovered by blood culture, death five months later
13	Mrs Dr J	68	125	58	67	115	Diastolic murmur over Erb's point, moderate grade aortic insufficiency with compensation
14	Miss J C	69	100	58	42	72	Amebic dysentery in 1903, uncinariasis in 1910, never completely recovered, now severe secondary anemia, hemoglobin 20, red blood cells 2,290,000, stools contain <i>Amoebae coli</i> , few distoma eggs, few hooklets of uncinaria, urine negative, systolic murmur over aorta transmitted to carotid, sclerosis of arch Periodic bleeding from right tuberculous kidney for seven years, secondary anemia, hemoglobin 25 per cent, reds 2,500,000, systolic blow over apex and base Five months before death

TABLE 4—MYOCARDIAL AND VALVULAR LESIONS WITH DECREASED HEART LOAD RATIO

No	Name	Age	S P	D P	P P	Cardiac Load Per Cent	
1	Mrs L E C	64	170	130	40	30	Same as Case 17, Table 1, syncopal attacks, angina, suffocation, cardiac cough, systolic murmur at apex, left ventricle hypertrophy, dilatation, arrhythmia, 12/27/13 Death from angina, 10/13/14 Enormous cardiac hypertrophy with dilatation, thrill over apex with systolic murmur, absolute arrhythmia, rate 164, positive venous and liver pulse Death three months later Systolic blow at apex, perpetual arrhythmia, cardiac dilatation, edema of limbs, swollen liver, 7/15/14 Disappearance of edema with compensation, 9/3/14 Hydropericardium, hydrothorax, alcoholic cirrhosis of liver, cardiac dilatation, death one week later Dyspnea on exertion and weakness, heart dull tones over all, displacement of apex to left, dilatation Congenital heart lesion, probably patent ductus arteriosus, hypertrophy and dilatation, three days before death Mitral regurgitation, perpetual arrhythmia, pulsus alternans, cardiac dilatation, in bed six months, general anasarca, 1/12/15 Positive venous pulse neck, 2/20/15 Death five months later Old healed fibroid phthisis, myasthenia gravis, in bed twelve months End of third week typhoid, temperature normal, marked periodic delirium with exhaustion, eventual recovery Septicopyemia, multiple septic thrombi (staph aureus); pulse 170 two hours before death
2	Miss M S	27	108	82	26	31	
3	Mrs E H	73	125	90	35	35	
4	F W C	73	150	95	55	58	
5	Mrs J C McF	77	100	75	25	33	
6	K M	54	140	105	35	33	
7	Mrs F W	12	98	88	10	11 5	
8	Miss M W	27	125	100	25	25	
9	C McC	27	125	105	20	19	
10	Miss J G	38	90	75	15	20	
		48	105	95	10	10	
		40	80	65	15	23	

3 Since the diastolic pressure represents the constant pressure between systoles, it is a better index of peripheral resistance and of hypertension than the systolic pressure. A sustained diastolic pressure of 105 to 110 or above signifies hypertension, irrespective of the height of the systolic pressure. The diastolic is less influenced by physiologic factors than the systolic pressure.

4 In arterial hypertension incident to myocardial and valvular lesions, the pulse pressure and heart-load are increased as a rule, the overload factor averaging 46 per cent in the twenty-four patients of the cardiac hypertension group. In this group the diastolic pressure was persistently lower than in the cerebral hypertension group while the pulse pressure was increased. This produced an increased ratio between these two pressures, representing the expenditure of increased energy on the part of the myocardium in an attempt at compensation, with a consequent increase in the heart-load percentage. The greater the overload factor the greater is the apparent subsequent danger of myocardial exhaustion, dilatation, and its sequelae.

5 In the cerebral hypertension group the diastolic pressure is persistently high, from 120 to 160. This group comprises the nephritic cases, so-called, with symptoms of polyuria, albumin, casts and edema. The pulse pressure is not so greatly increased, as a rule, and the heart-load percentage is within normal limits of 40 to 60 per cent. The term cardiorenal disease applied to patients with cardiac manifestations in nephritis is a misnomer. Cardiac symptoms are many times present in such cases but the manifestations and terminal events of vascular disease associated with disturbed renal function are more cerebral than cardiac. If any compound name is applied descriptive of the condition, the term cerebrorenal would be more approximate. The term Vascular Disease, however, covers the ground more completely.

6 In acute circulatory failure due to shock, including hemorrhage, in an individual with a strong acting heart, the diastolic pressure is decreased, while the pulse pressure is increased, since the heart is exerting all its force in an endeavor adequately to supply the periphery with blood. This endeavor is a compensatory effort, since the arteries may be more or less emptied in shock. The rapid pulse rate and increased respirations are likewise compensatory efforts. When the heart muscle has eventually exhausted itself, the systolic pressure falls, which results in a lessened pulse pressure until there is little leeway between the diastolic and systolic pressures. The heart at this point fails to move sufficient blood to the periphery to supply the respiratory and cardiac centers and its work ceases.

7 In circulatory failure due to cardiac dilatation or myocardial degeneration incident to acute or long continued illness, the systolic

pressure falls and tends to approximate the diastolic pressure, with the result that the pulse pressure is decreased. The sequelae above mentioned soon appear and death occurs from insufficient blood supply to the respiratory and cardiac centers.

8 In acute infections a sustained pulse pressure warrants a more favorable prognosis, as a rule, than a low pulse pressure, other things being equal, although the change from normal to low pulse pressure in circulatory failure may occur very rapidly. As a rule, the lower the pulse pressure, the greater the danger of circulatory failure.

9 Measures directed to the reduction of blood pressure by diet, habits, venesection and vasodilators are usually indicated in the cerebral hypertension group because of the high diastolic pressure, but are rarely indicated in the cardiac hypertension group. The high systolic pressures in the cardiac hypertension group are compensatory measures and rest, digitalis, strophanthin, camphor or caffeine are indicated when the heart muscle shows signs of fatigue.

THE TREATMENT OF CARDIAC INSUFFICIENCY BY A NEW METHOD OF EXERCISE WITH DUMB-BELLS AND BARS

THE CIRCULATORY REACTION TO EXERCISE AS A TEST OF THE HEART'S FUNCTIONAL CAPACITY *

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Brilliant as has been the advance in our knowledge of the pathology and diagnosis of cardiac disease during the last decade, therapeutics in this field are practically the same as they were twenty years ago, and consist chiefly in rest, diet, and digitalis

The possibility of developing the inherent power of the heart muscle was affirmed many years ago by Oertel, who used the very arduous exercise of hill climbing for this purpose. Since then the Nauheim school has been the chief exponent of the treatment of cardiac insufficiency by exercise and baths. The literature on these methods is meager, and judging from the scarcity of published reports, but few physicians in this country have been enough impressed with their value to give them a trial. Possible reasons for this are the elaborate outfit required for certain of them, lack of knowledge of the various special exercises, and more than anything else, perhaps, our inability to form an accurate estimate of the patient's cardiac efficiency. No method of increasing the strength of the heart muscle can be carried out in any but the most empiric way, nor can the results be correctly appraised if we do not first possess a fairly reliable test for determining the heart's functional capacity.

Before treating patients with cardiac insufficiency by the new method of exercise referred to in our title, it seemed essential, therefore, to investigate the various tests for cardiac efficiency which have been proposed, although the validity of each has been questioned and no one has met with general acceptance.

In 1905, Graupner originated a test consisting in deductions made from frequent observations of the pulse and systolic blood pressures after measured amounts of work, performed by means of an ergometer (that is, a form of stationary bicycle). His plan seemed peculiarly well adapted to our ends, for the exercises we used were of a kind

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that permitted a fairly accurate estimation of the amount of work performed. So we carried out Graupner's test in 150 experiments on fifteen normal people, using our exercises instead of the ergometer

EXPERIMENTS ON NORMAL PEOPLE

The pulse rate, systolic and diastolic pressures¹ were first taken. Then a measured amount of work was performed and the pulse rate and blood pressures were taken immediately after the cessation of work, and every one or two minutes thereafter, by the same observer. Then the same procedure was repeated with an increased amount of work.

Charts 1 and 2 show the type of reaction we invariably found. Directly after a moderate amount of work, the systolic blood pressure was raised and the pulse accelerated, both then rapidly falling to and below the figures noted before the work began. The rise was proportional to the amount of work, the time in which it was performed and to the individual's physique and muscular training. As soon as the work exceeded a certain amount, which varied for different individuals, we regularly found that the systolic blood pressure did not reach its highest point immediately after work, but a minute or so later at a time when the pulse rate had dropped back toward normal. The amount of work sufficient to produce this delay in the systolic blood pressure's reaching its maximum was generally accompanied by hyperpnea (in one person by vertigo and nausea), and the subject of the experiment was conscious that he had done a hard bit of work, sometimes unpleasantly so.

The physiologic explanation of this phenomena is still obscure. We know that during exercise the pressure in the aorta mounts rapidly, making the emptying of the left ventricle increasingly difficult. The exercise continuing, the pressure falls slowly, thereby relieving the strain on the ventricle. Just what part dilatation of the skin vessels or the splanchnic area plays in causing this fall we do not know, but it is evidently a defensive reaction to prevent the left ventricle from becoming insufficient.

Graupner² measured the blood pressure at frequent intervals in patients with cardiac insufficiency during and after increasing quantities of work, and showed that when the work reached a certain amount the pressure fell slowly, and, the work stopping, there ensued the delayed rise we have observed. He noted also that the harder the work, the more marked the subsequent delay, until, finally, in heavy

² Graupner. *Deutsch med Wchnschr*, 1906, No 26, p 1028

¹ After making numerous measurements of the diastolic pressure we found them of no value for our purpose and so omitted them.

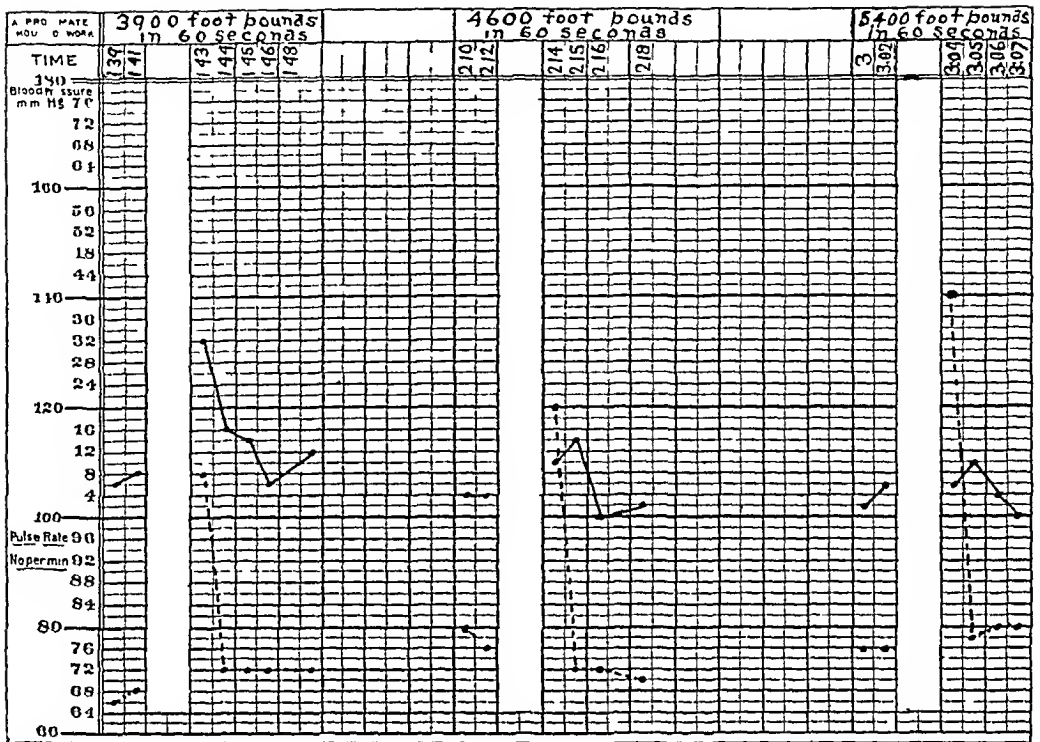


Chart 1—Type of reaction in normal persons after measured amount of work

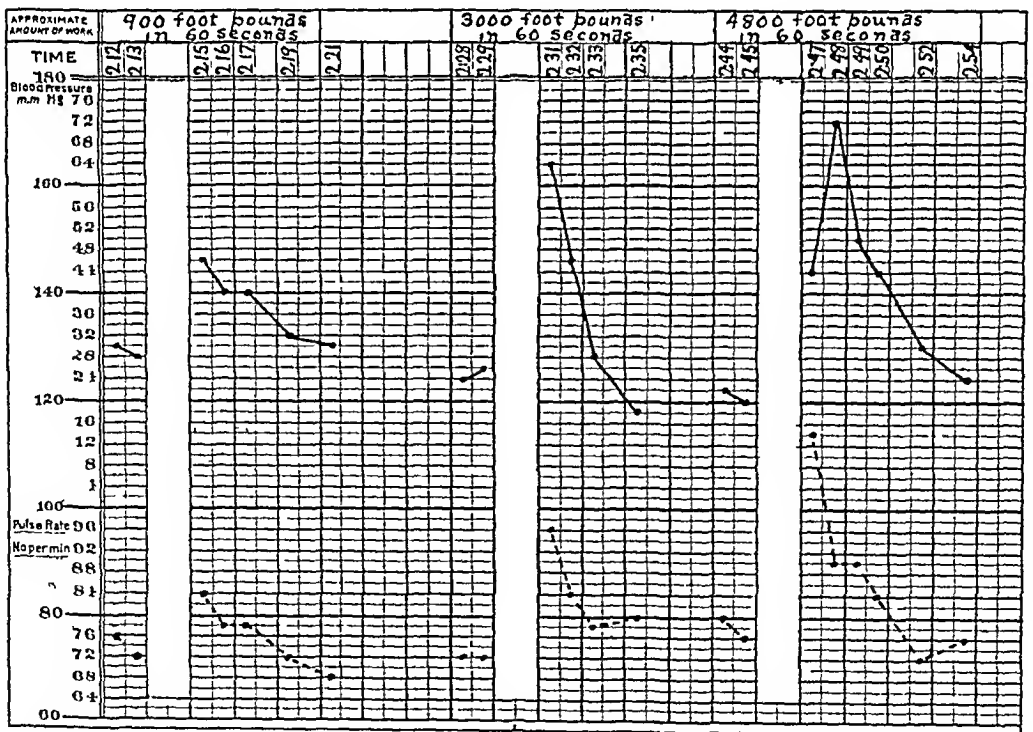


Chart 2—Reaction noted in normal persons after moderate amount of work

work the pressure immediately after was lower than before, and slowly returned to and above the original level

The exercise incident to an active physical life must frequently produce this delayed rise and the fact that damage is rarely done to the heart shows the efficiency of this protective mechanism We found that one week's training of a normal person would increase markedly the quantity of work he could do before a delayed reaction was produced

TEST FOR ESTIMATING THE HEART'S FUNCTIONAL CAPACITY

As a result of our experiments on normal people we were inclined to believe that in certain deductions made from the pulse and blood-

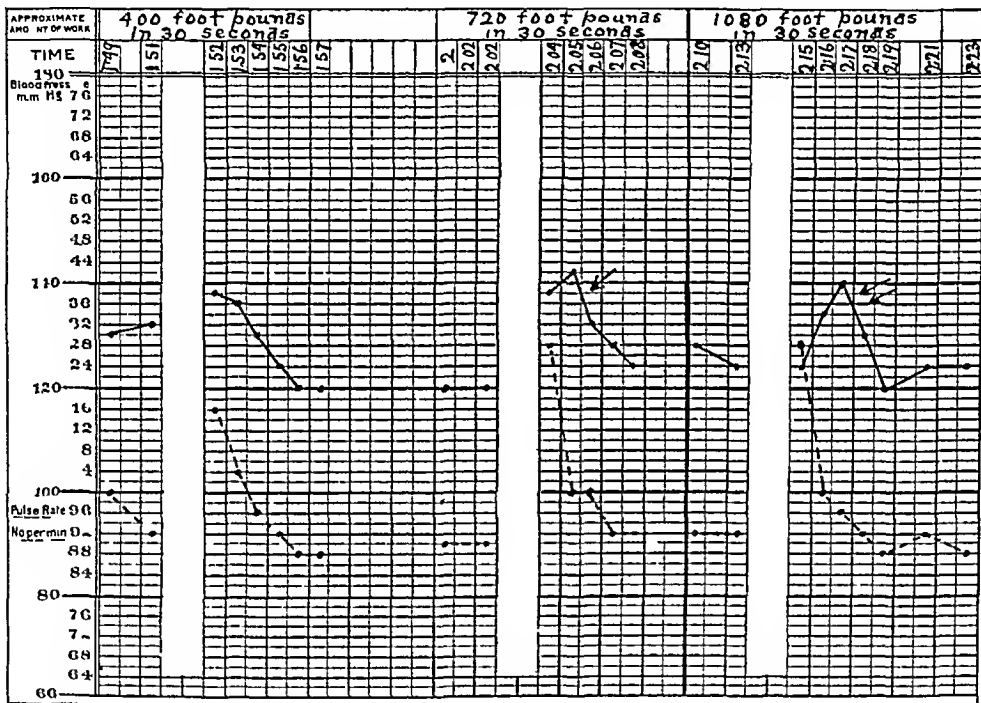


Chart 3—Effect of overtaxing left ventricle

pressure reactions to a measured amount of work, we possessed a valid test of the heart's functional capacity, even though we had no proved physiologic basis for this assumption As soon as the quantity of work was sufficient to produce a delayed reaction, we considered that we had overtaxed the heart's reserve force at that particular time and secured a measure of its efficiency As shown in Chart 1, if 3,900 foot-pounds of work performed in 60 seconds is followed by a rapid fall in blood pressure, and 4,600 foot-pounds of work in 60 seconds is followed by a delayed reaction, the functional capacity of that heart may be expressed as an ability to supply the amount of blood to the muscles necessary for doing between 3,900 and 4,600 foot-pounds of work in 60 seconds

The validity of this test of the heart's functional capacity unexpectedly received confirmation during the study of five patients suffering from angina pectoris. While estimating their cardiac efficiency we found in four of them that just as soon as work sufficient to cause a delayed rise in blood-pressure was given, a slight anginal attack was produced. After resting some minutes each patient was then given work increased by several hundred foot-pounds. A more marked delay in the blood-pressure rise and a more marked anginal attack was produced. In other words the overtaking of the left ventricle was evidenced clinically not only by the blood-pressure reaction but almost simultaneously by the angina. Chart 3 depicts this incident in one of the angina cases.

Accordingly we adopted this method of frequent pulse and blood-pressure determinations following a measured amount of work, as a guiding principle in the treatment of cardiac insufficiency, and it has worked out so well that we feel the validity of this criterion of the heart's efficiency has been practically established.

The pulse and blood-pressure curves we obtained after measured amounts of work differ in several very important points from Graupner's results and these differences do much to invalidate Graupner's conception of the essentials of his test. Our conclusions as to the import of the pulse and blood-pressure curves are naturally quite different from his, so different that our test cannot properly be called the Graupner test. In a later article we shall discuss this matter at greater length.

METHOD OF EXERCISE

The new method of exercise which we have been trying out this past year is new only in its application to cardiac insufficiency. It was devised many years ago by the senior author, Dr. Teschner, and has been used by him constantly in the practice of orthopedics. Several of his patients were suffering also from chronic valvular disease with cardiac insufficiency and he noted a marked improvement in their circulatory symptoms, attributable apparently to these exercises, so we were encouraged to experiment with them on a series of patients suffering from various cardiac disorders.

The apparatus used consisted of dumb-bells weighing from 3 to 25 pounds each and steel bars varying from 10 pounds upward in weight, with which different movements of flexion and extension were carried out. It was possible to measure the approximate number of foot-pounds of work performed in each exercise.

In treating our patients we followed this routine, 50 or 100 foot-pounds of work was given with a pair of 5 pound bells by pushing them alternately above the head. The pulse and blood pressure were

taken before and every minute after the exercises. If they showed a normal type of reaction, in a few minutes another piece of work was given, increased by 50 or 100 foot-pounds through using heavier bells. Sooner or later, we reached an amount of work which was followed by a delayed rise in blood pressure and we knew that the functional capacity of the patient's heart had then been exceeded. We found that many of our patients showed a cardiac efficiency of only a few hundred foot-pounds, which contrasted strikingly with the efficiency of a normal heart, which may measure as much as 7,000 foot-pounds performed in two minutes.

The daily exercise of our patients was arranged as follows. Having found in a given patient that 800 foot-pounds produced a delayed rise, his future work was limited to 700 foot-pounds for a period of seven days. Each day he was given this 700 foot-pounds to do from four to six times, with five or ten minutes rest in between, so that about an hour was used for the exercise period. At the end of seven days the heart's functional capacity was again tested and, if it had increased, the work for the next week was kept just below the amount that produced a delayed reaction.

As the patient's heart increased its efficiency, and the increase was often surprisingly rapid, various other exercises were added to the initial one of pushing dumb-bells above the head, exercises which utilized the trunk muscles and enabled us to increase markedly the number of foot-pounds performed without tiring excessively any one group of muscles. These were the swing, in which a bell is swung from the floor above the head and down again, the elbow and wrist being fixed, and bar work in which a steel bar is pushed above the head, the patient standing, or lying on the back. Each movement was repeated from 10 to 20 times, the patient being carefully instructed not to hold his breath while exercising on account of the pressor effect of a closed glottis. The time consumed in each form of exercise varied between 30 and 120 seconds. Patients were frequently conscious of improvement after six treatments. We usually gave them from twenty to thirty treatments. Sometimes we were in doubt as to whether a delayed reaction had occurred, generally in patients with fibrillating hearts. A repetition of the exercise with a slight increase of work would always clear this up. Sometimes the pressure after work was found to be lower than before. This is to be regarded as an extreme type of delayed reaction and means that the heart has been decidedly overtaxed by the preceding work. The production of one or two delayed reactions in a patient with cardiac insufficiency never seemed to have any harmful result.

The time required for the pulse rate and blood pressure of a delayed reaction to return to the previous level was a distinct aid in estimating the condition of the heart muscle. In one of our patients, who subsequently died with double mitral, double tricuspid and double aortic lesions, and a cardiac efficiency of but 200 foot-pounds in thirty seconds, ten to twenty minutes would almost always elapse before the return to normal of a delayed reaction.

PATIENTS SELECTED FOR TREATMENT

We selected for treatment ambulatory patients with chronic valvular or myocardial disease and varying stages of decompensation. Any suggestion of an acute process, any history of recent emboli or a persistently high blood pressure was considered to be a contraindication for the exercise treatment. Many of the patients had entered the hospital suffering from an acute insufficiency and had had the usual treatment of rest, diet, and digitalis. As soon as they were able to be up and walk around, they were given the exercises.

PATIENTS WITH MITRAL LESIONS

Table 1 summarizes our results in six of these patients. Three patients whose histories follow showed marked improvement.

TABLE 1—SUMMARY OF RESULTS IN SIX PATIENTS WITH MITRAL DISEASE

No. and Name	Age	Initial Cardiac Capacity foot pounds	Final Cardiac Capacity foot pounds	Initial Lung Capacity cu. in.	Final Lung Capacity cu. in.
1 T	40	150	520	70	96
2 F D	53	150	600	70	110
3 J T	28	?	?	162	180
4 B	31	75*			
5 P	55	120	280	50	62
6 D	24	100-200	525	?	?

* Exercise discontinued after five lessons.

Three patients whose histories follow showed marked improvement.

CASE 1—M T (Patient 1), a woman, aged 40, had been sick intermittently for a year, suffering from dyspnea and swelling of the feet and abdomen. On her second admission to the hospital she was cyanosed and orthopneic, her legs were much swollen, the liver extended six inches below the costal margin, there was free fluid in the abdomen and a small amount in each pleural cavity. Her heart showed a double mitral lesion and auricular fibrillation. After being treated with digitalis she was able in a few weeks to get around the ward. Several weeks later the exercise course was begun and she received fifty-eight treatments.

Twice the exercises were suspended and she was given digitalis (12 drams of the tincture altogether). After these two interruptions she improved steadily.

The edema of the legs subsided, the swelling of the liver lessened, and her strength returned. Her cardiac efficiency increased from 150 foot-pounds to 520 foot-pounds, and her respiratory capacity from 70 cubic inches to 96 cubic inches. Today (four months after stopping the exercises) she is doing her housework and feels "better than she has for years."

CASE 2—F D (Patient 2), a laborer, aged 53, had suffered from dyspnea and swelling of the ankles for a month before admission. On entering the hospital he was cyanosed and orthopneic. There was pretibial edema, fluid in the right pleural cavity and the liver was enlarged. His heart showed a mitral regurgitation and auricular fibrillation. Twenty-five ounces of clear fluid was taken from the right chest, and he received altogether, 9 drams of tincture of digitalis. Seven weeks later his exercise was begun. He had twenty-six treatments and improved markedly. His cardiac efficiency increased from 150 foot-pounds to 600 foot-pounds, and his lung capacity from 70 to 110 cubic inches. He went to work immediately after discharge, and did light work steadily for six weeks and then his dyspnea and swelling of the ankles returned. His breakdown was due to his shoveling snow for six hours one night after working all day. He recovered after three weeks stay in the hospital and began work again.

CASE 3—J T (Patient 3), a barber, aged 28, had a history of dyspnea, swelling of the ankles and occasional pulmonary infarction extending over three years. He had a double mitral lesion and auricular fibrillation. He improved markedly in the exercises and remained well for three months. Then he had another pulmonary infarct and decompensation followed.

Three patients did not do well. In one the treatment had hardly started (but five lessons were given) when we had to stop. Another improved slowly and then retrograded. This latter patient left the hospital against advice two weeks after treatment was discontinued, but returned in ten days and died twelve hours later. The necropsy showed an enormous heart with double mitral, double tricuspid and double aortic lesions. A third patient, a woman aged 55, with chronic bronchitis, a double mitral lesion, auricular fibrillation, and rather high blood pressure, improved slightly and then retrograded. She suffers now, two months after her last treatment, from recurring hydrothorax, shortness of breath and pretibial edema.

TABLE 2—SUMMARY OF RESULTS IN PATIENTS WITH MYOCARDITIS

No and Name	Age	Initial Cardiac Capacity foot pounds	Final Cardiac Capacity foot pounds	Initial Lung Capacity cu in	Final Lung Capacity cu in
1 P R	39	700	3,000	215	278
2 K	64	3,000 1,400 400	4,800	172	178
3 O B	54	800	1,600	?	?
4 D	56	?	?		

PATIENTS WITH MYOCARDITIS

CASE 4—P R (Patient 1, Table 2) This was a most interesting case in a laborer, aged 39, with splendid muscular development, who contracted bronchitis on Oct 17, 1914. For two weeks he complained of cough, weakness and shortness of breath. On Oct 29 he lifted one end of a cask weighing 1,200 pounds. He was immediately conscious of palpitation, and on trying to work again became very short of breath. He was helped to his home and the next day was admitted to the hospital. He was orthopneic, markedly cyanosed, and his ankles were swollen. His heart was rapid, regular, and showed at the apex

a gallop rhythm and systolic murmur. The lungs were clear. He was given 0.0005 of strophanthin intramuscularly and later received digitalis, 5 drams of the tincture, altogether. On November 5 he was up in a chair and the digitalis was stopped. Four days later his exercises were begun. He received thirty-four altogether, and improved remarkably, his cardiac capacity increasing from 700 foot-pounds in forty-five seconds to 3,000 foot-pounds in seventy-five seconds. Today he is doing light work and feels well.

Chart 4 represents his electrocardiograms, the first taken November 7, two days after stopping digitalis. His exercises were begun on November 9 and on December 3 the second electrocardiograms were taken. On November 7, T_1 and T_2 were directed downward. On December 3, T_1 and T_2 were directed upward. Also P was much higher on December 3 than on November 7. The initial reversal of T_1 and T_2 may have been, as A. E. Cohn has pointed out, a digitalis effect, or it may have indicated, as Einthoven holds, a damaged heart muscle. The change in the T waves following the exercises and the marked

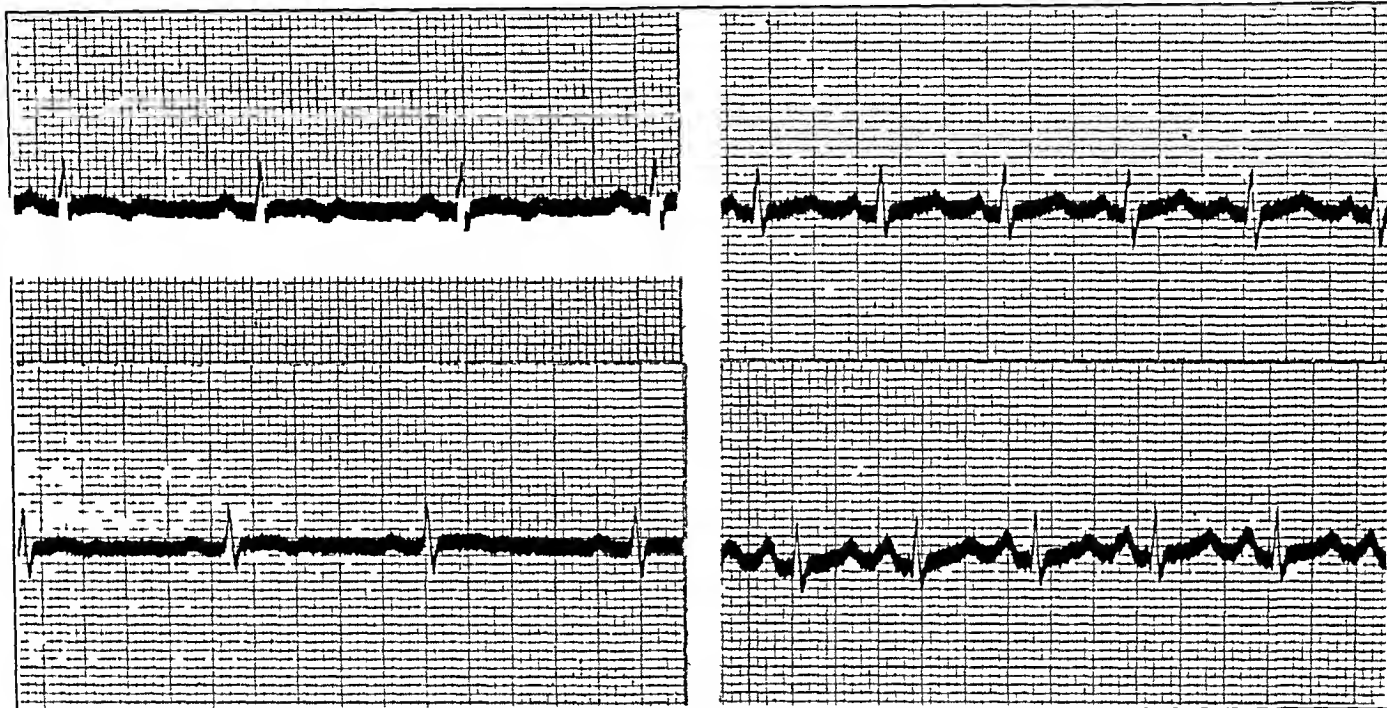


Chart 4—Electrocardiogram of Patient P. R. Leads 1 and 2 (at left) taken Nov 7, 1914, two days after stopping digitalis. Leads 1 and 2 (at right) taken Dec 3, 1914.

clinical improvement may have been due either to the exercises or to the release of the heart from digitalis influence. In regard to the significance of the increase in the height of P, it may be said that cases of compensated mitral stenosis generally show a large P wave.

CASE 5—K (Patient 2, Table 2), was a business man, aged 64, who had no symptoms referable to his heart, but complained of occasional attacks of vertigo, accompanied by increased blood pressure. His electrocardiograms showed some heart muscle involvement, chiefly left ventricle hypertrophy. He was given a course of twenty-one exercises to see if we could influence the form of the cardiogram. The estimation of his cardiac efficiency showed a peculiar result. The first day it was 3,000 foot-pounds in sixty seconds. Two days later it was 1,400 foot-pounds in sixty seconds, and two days still later it was but 400 foot-pounds in thirty seconds. He felt perfectly well and we could not explain this surprising decrease. From that time on by carefully grading his exercise, his cardiac efficiency increased steadily until it reached 4,800 foot-pounds in sixty seconds. His electrocardiograms showed no changes.

CASE 6—O B (Patient 3, Table 2), was a retired business man, aged 54, suffering from angina pectoris. He complained of shortness of breath and slight anginal attacks generally caused by walking or mental excitement. He was overweight, examination of his heart was negative and his Wassermann test was negative. His cardiac efficiency increased from 800 foot-pounds to 1,600 foot-pounds, but his angina was not improved. His electrocardiogram showed slight changes.

CASE 7—D (Patient 4, Table 2), was a woman, aged 56, suffering from dyspnea on exertion. She was obese, weighing 218 pounds. Her heart showed an auricular fibrillation but no murmurs. Her blood pressure ranged between 180 and 210 mm Hg. The urine was negative. She showed no improvement after twenty-eight exercises.

PATIENTS WITH AORTIC REGURGITATION

We treated three patients with this lesion, all young men under 25 with high initial cardiac capacities and with no evidence of insufficiency except shortness of breath on exertion. They improved much

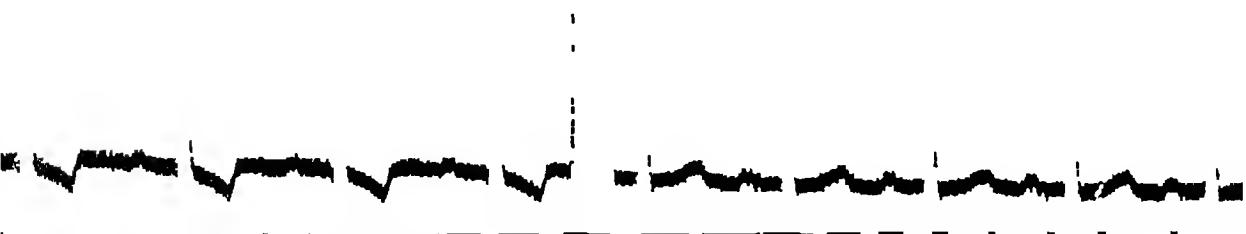


Chart 5—Electrocardiogram in case of aortic regurgitation. Lead 1 (at left) taken before the exercise course. Lead 2 (at right) after exercise course.

more quickly than did the patients with mitral disease, feeling decidedly better after four or five treatments. Their youth, the slight degree of decompensation, and the intenser effect of exercise on the left ventricle, explain the rapidity of their improvement.

Chart 5 shows the electrocardiograms of one of these patients, taken before and after the exercise course. He had received no digitalis for months before the first electrocardiogram. It shows an inverted T_2 wave which becomes erect in the second one, at which time he showed a marked clinical improvement. R_2 and R_3 were taller in the first, than in the second electrocardiogram.

Chart 6, represents the electrocardiograms of another aortic patient taken before and after eleven treatments with exercise. They show a marked increase in the height of R_1 and an increase in the negativity of R_3 . The average height of R_1 in the first was 10 mm, in the second 25 mm. R_3 in the first measured -6 mm, in the second, -15 .

The electrocardiograms of a third patient showed an increase of R_2 from 18 mm to 27 mm, and of R_3 from 8 mm to 16 mm.

These last two patients showed an increase in the height of the R waves accompanying clinical improvement, while Patient 1 showed a decrease in the height of his R waves

We took electrocardiograms of all our patients before and after the exercise treatment, and the four described are the only ones showing decided changes. But one patient showed changes pointing to an increased left ventricular hypertrophy

SUMMARY OF HEART CASES

Nine of the thirteen patients treated showed marked improvement attributable apparently to the exercises, for with one exception, no other treatment was given during the exercise course. Three of the

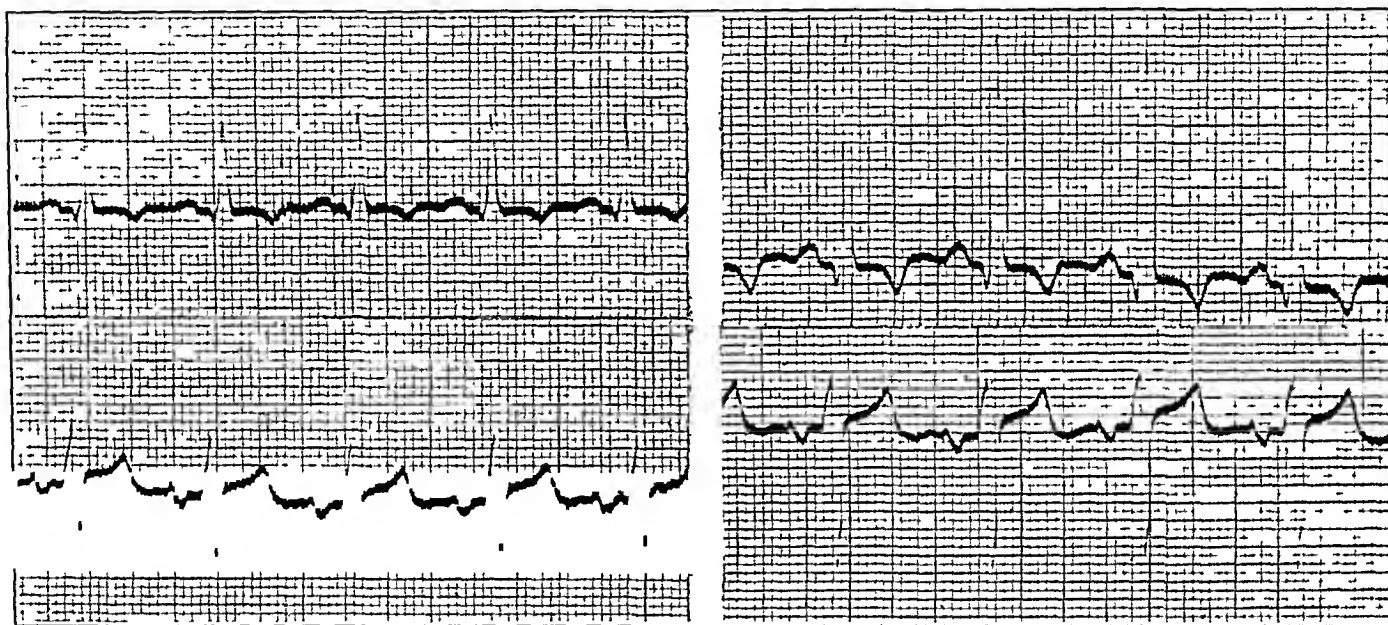


Chart 6—Electrocardiogram in case of aortic regurgitation (at left) before exercise, and (at right) after exercise

patients, who did not improve suffered from mitral disease with marked decompensation and showed very low initial cardiac and respiratory capacities

PHYSIOLOGY OF EXERCISE

The marked increase in the heart rate and raising of the systemic blood pressure caused by exercise in general are undoubtedly the chief physiologic factors in producing the many beneficial effects of muscular activity. Increased ventilation of the lungs also plays an important rôle

In our system of exercises the pulse rate is increased and the blood pressure raised for very brief periods of time. The respiration is quickened likewise for a few seconds. Whether this transient excitation of the circulatory system repeated six or seven times in the course

of an hour would have any appreciable general effect on a normal person was a question which suggested itself when making our earlier experiments to secure a valid test of the cardiac efficiency. Accordingly we gave the exercises to six normal people for a month, using heavier weights, and found to our surprise that the benefit to their health (appetite, digestion, sleeping and general efficiency), was marked and unmistakable. The improvement in the heart patients must have been due to the same physiologic cause. To be more specific, the raising of pressure in the aorta improves the coronary circulation and peripherally it causes a more rapid blood flow through each organ. Also the help to the venous circulation afforded by alternate relaxation and contraction of the muscles is considerable. The lymphatic flow in particular is aided by this muscular action, thereby bringing more quickly the end-products of metabolism to the blood stream and so to the excretory organs. Also the increase in lung capacity which our exercises seem peculiarly adapted to bring about, aid materially in improving the heart action and the pulmonary circulation. This increase amounted to 36 per cent in four of our patients with mitral disease. The psychical effect on a cardiac patient of actually doing physical work and feeling better rather than worse for it, must not be overlooked.

It is hardly probable that our results were due in any way to increasing the cardiac hypertrophy already existing in our patients. Failure to demonstrate any changes in the electrocardiograms indicating increased hypertrophy with one exception, and the absence of change in the physical signs, and the fact that the actual total working time of each patient was not over five to eight hours for the entire course, all militate against such a supposition.

COMPARISON OF OUR EXERCISES WITH RESISTANCE GYMNASTICS

Resistance gymnastics is the chief form of exercise used today in cardiac insufficiency and forms an important part of the Nauheim treatment. A comparison with our system of exercises might be of interest.

The most striking feature of the exercises we advocate is their concentration. Each series of movements lasts from thirty to one hundred and twenty seconds and is followed by a rest from five to ten minutes. It would be quite possible to spread the work over from ten to fifteen minutes so that the patient would accomplish the same number of foot-pounds in the longer period of time. This we have done but found there was a much slighter effect on the pulse and blood pressure. If the rise in blood pressure and increase in heart rate are the essen-

tial physiologic causes of the benefit derived from exercise, then our present concentrated form of exercise must be far more efficient than any other, *provided always* that we can guard against too high a blood pressure and too rapid a pulse. We feel convinced that our test, the validity of which we took such pains to establish, protects us against such danger.

On reading the description of resistance gymnastics in the last edition of Schott's "Treatment of Chronic Diseases of the Heart," one is impressed with the extreme gentleness of the exercise, and the impossibility of measuring the work performed, slight though it is. On page 253, there is a chart showing the effect of the exercises on a low blood pressure. The systolic pressure taken before exercise by palpation is 115 mm and pulse 82. Taken after 25 minutes of exercise the pressure is 120 (by palpation) and the pulse 72. It is needless to say that a variation of 5 mm in the systolic pressure is trivial and will be found in any normal person who is sitting quietly in a chair. Also the margin of error in taking blood pressure by palpation frequently amounts to more than 5 mm. On page 55, a chart is reproduced showing that the same exercises *reduce* high blood pressure. Before exercise the systolic blood pressure was 175 and pulse 81; after thirty minutes of exercise the pressure was 160 mm and pulse 62. If readings are made every five minutes on a patient with hypertension, sitting quietly in a chair, they will be found to vary as much as 10 mm. If a patient talks they will vary much more.

We have given our exercises cautiously to ten patients with high blood pressures and found that invariably a very small amount of work caused a *rise* of pressure which was followed by a fall to and below the preexercise figure.

That any form of exercise can raise a low pressure and lower a high pressure, the readings being taken at synchronous periods during or after exercise, is physiologically incomprehensible.

The only reasonable explanation of the charts just described is that they represent normal variations in blood pressure and would have been found whether or not the resistance exercises were carried out.

The good results unquestionably obtained at Nauheim, must be caused by the effervescing baths, for charts published in the above-mentioned work show a more marked pressor effect from the baths than from the resistance gymnastics.

CONCLUSIONS

- 1 The validity of the postexercise blood-pressure test of the heart's functional capacity has been established.

2 Although our experience is limited to a small group of patients, we feel that our system of exercise affords a valuable adjunct to the means already at our disposal for treating cardiac insufficiency

We are much indebted to Dr H B Williams for doing the electrocardiographic work We wish also to express our appreciation of the very material help rendered by Dr H S Valentine and Dr F W Fiedler in carrying out the work recorded above

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THE RESISTANCE OF THE RED BLOOD CELLS TO HYPOTONIC SALT SOLUTION IN THE VARIOUS ANEMIAS

WITH OBSERVATIONS ON THE RESISTANCE AFTER ARSENICAL TREAT-
MENT, AND AFTER SPLENECTOMY¹

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The resistance of the red blood cells has been extensively studied in the last few years, in various connections. There seems to be a considerable discrepancy in the results of the various investigators as to whether or not the resistance to hypotonic salt solution is raised or lowered in primary and secondary anemias. The purpose of this paper is to report a somewhat larger series of cases with anemia than has before been studied, as it is felt that the discrepancies in the results of various investigators may have been due to the fact that not enough cases were studied.

There are different ways of studying the resistance of the red cells. The methods used have been three:

- 1 The physicochemical method, with hypotonic salt solution
- 2 The chemical method, with saponin or allied substances
- 3 The biological method, with specific hemolysins

It cannot be said that any one of these methods parallels the destruction of red blood cells in the body in cases of anemia. We know that such destruction is probably brought about by toxic substances, the exact chemical nature of which we do not know.

Bigland¹ says, "the popular physico-chemical procedure of hemolysis by means of hypotonic salt solution has a great objection—its artificiality. If it is wished to examine a patient's blood with regard to its resisting powers against the pneumococcus, is it any advantage to inject tubercle bacilli, and then draw conclusions from the results?"

With this we agree, and believe that the same applies to saponin, or to any specific serum, when used as a hemolytic agent. Hemolysis with saponin, with hypotonic salt solution, and with specific serums are probably three entirely different processes, and what holds for the one does not hold for the other, as has been shown many times.

* Submitted for publication July 1, 1915

¹ From the West Medical Service, Massachusetts General Hospital. Dr. Richard C. Cabot, Chief of Service, Dr. Roger I. Lee and Dr. William H. Smith, Visiting Physicians.

¹ Bigland. *Quart Jour Med*, Oxford, 1914, vii, No. 28, p. 369.

I do not intend to discuss hemolysis by saponin or specific serums at all, but to confine myself to experiments with hypotonic salt solution, bearing in mind that conclusions drawn from this form of hemolysis cannot be applied to the other two forms, nor directly to any phase of disease. In previous work, in general, investigators have used widely different methods, and this partly accounts for the variation of results.

The several factors concerned in the accuracy of the results are

1 The method of making up the dilutions of salt solution, whether accurately measured in burets, or by the "drop" method

2 The state in which the blood is examined, whether as washed cells or as whole blood

3 The proportion of blood cells to salt solution in each tube

4 The method of reading hemolysis

These discrepancies make it somewhat difficult to compare results. In 1902 Veyrassat² studied the resistance of the red cells in pernicious and secondary anemia, and found that in pernicious anemia it was decreased, but increased in secondary anemias.

In 1903, Ribierre,³ studying normal blood, found that initial hemolysis was at 0.44 per cent salt solution, complete hemolysis at 0.34 per cent. In 1907 Chauffard⁴ wrote his classical article on chronic family jaundice, in which he brought forward the fact that there was an increased fragility of the red cells in this disease. Everyone who has studied chronic family jaundice since has confirmed this observation. In the same year Chauffard and Rendu⁵ studied a series of 10 normal cases, and found that hemolysis began at 0.46 and was complete at 0.38. Paoloni⁶ found that there was always a diminution of resistance in anemia, whether primary or secondary. In normal blood, he found that hemolysis began at 0.44 and was complete at 0.36.

Ehni and Alexieff⁷ reported two cases of pernicious anemia with decreased resistance.

Weill and Dufourt⁸ believe that in the presence of any plasma harmful for them the red blood cells develop an increased resistance.

Jakuschewsky,⁹ coinciding with Weill and Dufourt, believes that there is increased resistance as long as toxic substances are circulating.

2 Veyrassat. *Lyon med.*, 1902, No. 25.

3 Ribierre. *These de Paris*, 1903, p. 106.

4 Chauffard. *Semaine med.*, Paris, 1907, p. 25.

5 Chauffard and Rendu. *Presse med.*, 1907, xv, 345.

6 Paoloni. *Policlinico*, Rome, 1913, No. 6, p. 243.

7 Ehni and Alexieff. *Compt. rend. Soc. de biol.*, 1908, lxiv, 1101.

8 Weill and Dufourt. *Presse med.*, xxi, No. 56, 565.

9 Jakuschewsky. *Russ. med. Rundschau*, 1904, No. 6, p. 345, *Folia Hematol.*, 11, p. 21.

in the blood Morawitz and Pratt¹⁰ found that in experimental anemias produced with phenylhydrazinhydrochlorid, there was increased resistance

Snapper¹¹ found that red blood cells obtained after severe hemorrhage were more resistant than those obtained beforehand, and that young cells were more resistant than older ones

McNiell¹² studied saponin hemolysis, and found that some cells which had an increased resistance to hypotonic salt solution, had a decreased resistance to saponin. This was especially true of blood from cases of obstructive jaundice

He also found that immersing the cells in hypertonic solution for a period of time increased their resistance. He found that in all cases in which there was a diminution in the number of red cells there was increased resistance to saponin, with the exception of pernicious anemia, which showed practically normal resistance

Bigland,¹ in six cases of pernicious anemia, found that the resistance was either normal, or very slightly decreased. In secondary anemia he found a slightly increased resistance

A criticism of all these results is that not enough cases were studied

TECHNIC

The method used in the cases studied at the Massachusetts General Hospital was as follows

About 6 c.c. of blood is withdrawn from the arm vein with a needle and glass syringe. This is transferred to a test tube half full of 0.5 per cent sodium citrate solution in 0.9 per cent sodium chlorid. The tube is then inverted two or three times to insure proper mixing. As soon as possible (certainly within three hours) the blood is centrifuged and the cells washed twice with 0.7 per cent sodium chlorid. As much of the supernatant fluid as possible is drawn off with a pipet, and the remaining blood cells are used in the test, without further dilution. The hypotonic sodium chlorid solutions are made up from a 1 per cent solution of chemically pure sodium chlorid and distilled water. The solutions run in strength from 0.70 per cent to 0.175 per cent, and are kept in tightly corked 100 c.c. bottles

Exactly 1 c.c. of each one of these solutions is drawn off in a pipet, and placed in a series of small test tubes, 0.05 c.c. of the blood cells is then run into each tube, from a small, accurately graded pipet, each tube is inverted twice and allowed to stand two hours at room temperature, at the end of this time the tubes are read. As initial hemolysis I have taken the point at which there is the first tinge of pink in the salt solution, as complete hemolysis the point at which there can no longer be seen any sediment of blood cells in the bottom of the tube. There is nothing difficult or complicated about this method, its only disadvantage is that it takes considerable time

10 Morawitz and Pratt *Munchen med Wchnschr*, 1908, 11, No 25

11 Snapper *Biochem Ztschr*, 1912, xliii, 256

12 McNiell *Jour Path and Bact*, London, 1911, xv, 56

NORMAL BLOOD

Nineteen normal bloods were examined and were found to have an average resistance of 0.457 for initial hemolysis, and 0.340 for complete. The figures for the most fragile normal blood were 0.475 (initial) and 0.375 (complete). The lowest point at which hemolysis began in any case was 0.425, the lowest point at which it was complete was 0.275. The lowest point at which hemolysis began in any case was 0.425, the lowest point at which it was complete was 0.275. The normal bloods seem to have a fairly constant resistance, the most constant figure being the point of initial hemolysis.

SECONDARY ANEMIA

Twenty-four cases of secondary anemia due to various causes, were examined. (See tables.)

In general, hemolysis in secondary anemia seems to start at a dilution somewhat less than it does in normal blood, and to extend over a larger number of tubes, so that the point of complete hemolysis is somewhat lower than in normal cases. In anemic bloods some of the cells seem less resistant than normal, some more resistant. The young cells have been thought to be the most resistant of all cells, but Pepper and Peet¹³ were not able to demonstrate any increase in resistance of the so-called "skewed" or reticulated forms, seen especially in anemic bloods, and certainly in cases of chronic family jaundice, in which from 20 to 30 per cent of the red cells are of this reticulated type,

TABLE 1—NORMAL BLOODS

	Initial Hemolysis	Complete Hemolysis
1	0.475	0.375
2	0.450	0.325
3	0.475	0.350
4	0.475	0.350
5	0.475	0.325
6	0.425	0.275
7	0.425	0.325
8	0.450	0.325
9	0.475	0.300
10	0.450	0.300
11	0.450	0.350
12	0.450	0.350
13	0.450	0.350
14	0.475	0.350
15	0.475	0.300
16	0.425	0.325
17	0.475	0.375
18	0.450	0.350
19	0.450	0.375
Average	0.457	0.340

¹³ Pepper and Peet. The Resistance of Reticulated Erythrocytes, *THE ARCHIVES INT. MED.*, 1913, **xii**, 81.

TABLE 2—SECONDARY ANEMIA

Diagnosis	Hgb, Per Cent	R B C	Initial	Complete
1 Carcinomatosis	50	2,904,000	0 525	0 300
2 Addison's disease	80	3,040,000	0 500	0 300
3 Retroperitoneal cancer	60	2,800,000	0 450	0 325
4 Cancer of stomach	75	3,700,000	0 550	0 300
5 Cancer of sigmoid	75	3,686,000	0 425	0 275
6 Cancer of colon	70	4,752,000	0 450	0 275
7 Pyelitis	75	4,352,000	0 425	0 275
8 Chronic nephritis	70	4,157,000	0 425	0 325
9 Cancer of stomach	70	3,936,000	0 450	0 300
10 Ulcer of stomach	50	2,676,000	0 475	0 275
11 Chronic nephritis	55	2,250,000	0 450	0 250
12 Cancer of stomach	55	3,760,000	0 475	0 300
13 Cancer of stomach	70	2,936,000	0 450	0 300
14 Myxedema	70	4,224,000	0 450	0 325
15 Pylephlebitis	75	4,500,000	0 425	0 325
16 Cancer of stomach	60	2,688,000	0 450	0 300
17 Nose bleed	65	3,440,000	0 475	0 275
18 Myxedema	70	5,332,000	0 475	0 350
19 Malaria	55	2,408,000	0 450	0 350
20 Debility	55	3,920,000	0 475	0 375
21 Arteriosclerosis	60	2,856,000	0 450	0 225
22 Syphilis	70	3,880,000	0 500	0 375
23 Chronic nephritis	55	3,080,000	0 475	0 375
24 Myxedema	70	3,656,000	0 450	0 375
25 Paroxysmal hemoglobin- uria			0 450	0 300
Average			0 475	0 322

TABLE 3—PERNICIOUS ANEMIA

	Hgb, Per Cent	R B C	Initial	Complete
1	55	1,696,000	0 550	0 400
2	40	1,376,000	0 475	0 300
3	65	2,896,000	0 500	0 300
4	70	2,000,800	0 500	0 325
5	55	1,680,000	0 475	0 300
6	30	1,200,000	0 475	0 325
7	55	2,832,000	0 450	0 325
8	75	3,000,000	0 450	0 325
9	70	2,500,000	0 475	0 300
10	60	2,215,000	0 400	0 275
11	60	2,760,000	0 475	0 300
12	25	800,000	0 475	0 250
13	50	1,344,000	0 475	0 325
Average			0 477	0 322

TABLE 4—MISCELLANEOUS

Diagnosis	Hgb, Per Cent	R B C	Initial	Complete
Splenic anemia	0 50	3,200,000	0 500	0 275
Splenic anemia	0 50	4,000,000	0 500	0 200
Banti's disease	0 70	3,108,000	0 475	0 375
Chronic family jaundice	0 80	4,120,000	0 600	0 400
Obstructive jaundice			0 400	0 225
Obstructive jaundice			0 400	0 175
Obstructive jaundice			0 425	0 275

there is no increase of resistance, quite the contrary. The average points of hemolysis for the secondary anemia cases were, 0.475 (initial), 0.322 (complete). The highest initial hemolysis was at 0.550, the highest complete hemolysis at 0.375. The lowest initial hemolysis was at 0.425, the lowest complete at 0.250. It will thus be seen that there are apparently no assured and constant values for the points of initial and complete hemolysis in the blood from cases of secondary anemia, although in general, the tendency is as stated above.

PERNICIOUS ANEMIA

Blood from 13 patients with pernicious anemia was examined. Several of these patients had previously had arsenic in some form, but most of them had had none for at least six months previous to testing their blood fragility. One case only had had salvarsan four days before the fragility test was done on his blood. This is important to note, for as will be shown later, arsenic may have a good deal of influence on the fragility.

The average for the pernicious anemia cases was 0.477 (initial), 0.322 (complete). The highest figures were 0.550 (initial) and 0.400 (complete). The lowest figures were 0.400 (initial) and 0.250 (complete). It will thus be seen that the average is about the same as for secondary anemia, but there may be more variation in the individual cases. It is interesting to note the case which showed the greatest fragility 0.500 (initial) 0.400 (complete). The patient was an Armenian woman with an easily palpable spleen and liver, and a great deal of brownish pigmentation. The blood picture was quite characteristic of pernicious anemia, with many megaloblasts and normoblasts, many macrocytes and microcytes, and much polychromatophilia and stippling. It corresponds very closely to the type of case to which Moffit has called attention, in which the picture is such that no other diagnosis than pernicious anemia is possible, but in which the spleen is much larger than in the ordinary case, with a good deal more pigmentation of the skin than is usually seen, and an increased blood fragility, somewhat approaching the type of anemia sometimes found in cases of chronic family jaundice.

Cases of splenic anemia, myelogenous and lymphatic leukemia, Banti's disease, chronic family jaundice, and obstructive jaundice were studied, but not enough cases of each group to warrant drawing any definite conclusions.

The figures for obstructive jaundice agree with those of other investigators, there is always a greatly increased resistance in obstructive jaundice, which may be due to the fact that the serum of jaundiced patients is hypertonic (it has been shown that by immersing red blood

cells in hypertonic solutions, the resistance can be increased), or to the fact that the cholesterol in the jaundiced serum may have a direct inhibitory effect on hemolysis. The fragility test is of practical value as a corroborative test in differentiating between obstructive and hemolytic jaundice, for as far as I know, there is always increased resistance in the former, and decreased in the latter.

It has been said that the hemoglobin content of the cell is the factor which governs cell fragility; with a low hemoglobin percentage there is a high resistance, and as the hemoglobin increases, the resistance decreases (Strasser and Neumann¹⁴).

It will be seen from the tables that this does not hold for the cases reported here, there is apparently no relation between the hemoglobin content of the cell and its resistance.

To recapitulate. The average points of hemolysis for normal bloods, pernicious and secondary anemias, are

Normal	0.457 (initial)	0.340 (complete)
Secondary anemia	0.475 (initial)	0.322 (complete)
Pernicious anemia	0.477 (initial)	0.322 (complete)

THE INFLUENCE OF ARSENIC ON HEMOLYSIS

In 1898, Bettmann,¹⁵ in a very comprehensive research on the effect of arsenic on the blood and blood-forming organs, found that in sub-acute arsenical poisoning, there was a lowering of resistance. In his work he did not use ordinary medicinal doses, but worked with larger toxic doses. In 1908 Gunn¹⁶ found that immersing red blood cells for an hour in a solution of arsenious acid (1 to 10,000) made them more resistant to hypotonic salt solution. In 1911 Gunn and Feltham¹⁷ continued these experiments and found that arsenic not only had a protective action against hemolysis with hypotonic salt solution, but also protected against hemolysis with cyclamin (a saponin-like substance), and sodium glycocholate. It was thought worth while to continue this work and it was done as follows:

1. A normal blood was run through in the regular way, with the regular amount of salt solution and blood, *plus* 0.05 cc 0.7% salt solution in each tube. Initial hemolysis 0.425. Complete hemolysis 0.350.

Then in a second series of tubes the procedure was the same, only substituting 0.05 cc of 0.7% salvarsan solution for the 0.05 cc of 0.7% salt solution. Initial hemolysis 0.425. Complete, 0.325.

In a second test 0.10 cc salt solution was used instead of 0.05 cc. Initial hemolysis 0.425. Complete hemolysis 0.300. When 0.10 cc of salvarsan solution was substituted for the salt, the figures were 0.400 (initial), 0.300 (complete).

In these four series there was, it is true, some increase of resistance in the tubes containing salvarsan, as shown by the reading of the initial and complete

¹⁴ Strasser and Neumann. *Med Klin*, 1909, No. 34.

¹⁵ Bettmann. *Ziegler's Beitr zur pathol., Anat.*, 1898, xxiii.

¹⁶ Gunn. *Brit Med Jour*, July 28, 1908.

¹⁷ Gunn and Feltham. *Brit Med Jour*, Jan 21, 1911.

hemolysis, but the most striking thing was that in each pair of corresponding tubes, all down the line from initial to complete, there was *always* much less hemolysis in the tubes containing the salvarsan

2 Normal blood (0.05 cc) + 0.05 cc 0.7 per cent salvarsan solution + 0.5 cc distilled water — *nearly complete hemolysis*

Normal blood (0.05 cc) + 1.05 cc 0.7 per cent salvarsan solution + 0.5 cc distilled water — *very slight hemolysis*

3 Anemic blood (0.05 cc) + 0.05 cc 0.5 per cent salt solution in each tube, 0.475 (initial), 0.400 (complete)

Same blood (0.05 cc) + 0.05 cc 0.05 per cent Fowler's solution (potassium arsenite) substituted for the 0.05 cc of salt solution, 0.400 (initial), 0.275 (complete)

Syphilitic blood (0.05 cc + 0.05 cc 0.5 per cent salt solution in each tube, 0.450 (initial), 0.375 (complete)

Same blood (0.05 cc) + 0.05 cc 0.5 per cent Fowler's solution substituted for the 0.05 cc of salt solution, 0.375 (initial), 0.275 (complete)

These results with Fowler's solution are very striking, and clearly prove that *in vitro*, at any rate, arsenic has a very definite inhibitory effect on hemolysis. *In vivo* the results are not quite so striking, but show the same thing to a less degree

In 4 cases of syphilis, the fragility of the blood was tested before and after 0.3 gm of salvarsan intravenously. There was exactly the same resistance before as after, the arsenic given had no effect whatever on the fragility. The amount of arsenic, however, in the 6 cc of blood taken for examination, is so infinitesimal (about 0.0006 gm), that it could hardly be expected to influence the fragility

In 3 cases of pernicious anemia treated with several doses of salvarsan the results were as follows

1 Before salvarsan	0.475 (initial)	0.300 (complete)
After seven doses of salvarsan	0.400 (initial)	0.275 (complete)
2 Before salvarsan	0.450 (initial)	0.325 (complete)
After five doses of salvarsan	0.425 (initial)	0.350 (complete)
3 Before salvarsan	0.400 (initial)	0.275 (complete)
After four doses of salvarsan	0.450 (initial)	0.275 (complete)

It is interesting to note that the general condition, and the red count and hemoglobin of the first two cases rose during the salvarsan treatment, and were unchanged in the third case

4 A case of pernicious anemia was given Fowler's solution for ten days, starting with 5 drops three times a day, and increasing 3 drops a day, until he was getting 36 drops in the twenty-four hours

The blood was examined before and after the course of Fowler's solution

Before	0.475 (initial)	0.325 (complete)
After	0.450 (initial)	0.275 (complete)

It would seem from the figures that arsenic in medicinal doses has a definite inhibitory action on hemolysis, *and it may well be that the beneficial effect of arsenic in the anemias is due rather to a prevention of hemolysis than to a stimulant effect on the bone marrow, a view which has been held by some writers*

CHANGES IN FRAGILITY AFTER SPLENECTOMY

Pel,¹⁸ in 1912, found in splenectomized dogs that there was an increased resistance of the red cells to hypotonic salt solution after splenectomy Karsner and Pearce¹⁹ confirmed this As far as I know, there are no data concerning fragility changes after splenectomy in human beings About the time that this work was being done, a number of ward patients with pernicious anemia were operated on, with removal of the spleen The blood fragility of these patients was studied before and after operation

1 Before splenectomy	0.475 (initial)	0.300 (complete)
8 days after splenectomy	0.450 (initial)	0.275 (complete)
21 days after splenectomy	0.500 (initial)	0.250 (complete)
2 Before splenectomy	0.475 (initial)	0.300 (complete)
15 days after splenectomy	0.450 (initial)	0.275 (complete)
50 days after splenectomy	0.700 (initial)	0.225 (complete)
3 Before splenectomy	0.475 (initial)	0.250 (complete)
15 days after splenectomy	0.475 (initial)	0.250 (complete)

These figures are somewhat contradictory, but in three of the cases the greatly increased resistance of some of the cells, as shown by the low figures for complete hemolysis, was striking It was noted in all these cases that a good many cells with the so-called "Jolly bodies" appeared in the blood after splenectomy It is possible that these cells may have been the cause of the increased resistance

CONCLUSIONS

1 The resistance of normal blood to hemolysis by hypotonic salt solution is fairly constant

2 The figures for pernicious anemia and for secondary anemia are practically the same In any given case of anemia, whether primary or secondary, the resistance may be high, normal, or low, there is no such constant finding as there is in normal blood In general, in both pernicious and secondary anemia, hemolysis is likely to begin sooner and end later than it does in normal blood

3 The hemoglobin content of the cell seems to bear no relation to its resistance

4 Arsenic definitely increases the resistance of the red cells and tends to inhibit hemolysis

5 Splenectomy increases the maximal resistance, it may decrease the minimal resistance

I wish to express my thanks to the members of the visiting staff for their interest during the course of the work, and for their many helpful suggestions

18 Pel *Deutsch Arch f klin Med*, 1912, cvi, Nos 5 and 6

19 Karsner and Pearce *Jour Exper Med*, 1912, xvi, 769

A STUDY OF A CASE OF AURICULAR FLUTTER*

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In 1887 McWilliam¹ produced a flutter in the auricles of the mammalian heart by means of faradic stimulation of the auricles. In 1908 Hertz and Goodhart² reported a human case in which the auricles were beating rapidly at a rate of about 230 per minute, but the ventricles were beating about 80. In 1911, Jolly and Ritchie³ applied the term of auricular flutter to those cases of rapid regular auricular contractions ranging from 250 to 350 per minute associated with partial or complete heart block, so that the ventricular rate was much slower.

Reports of similar cases have appeared in the medical literature since that time. Summaries of these cases with the addition of new ones have been made by Lewis⁴ in 1912, and more recently by Ritchie⁵ in 1914. At present this cardiac condition is well recognized as a clinical entity, and appears in the modern textbooks on cardiac diseases such as Lewis's⁶ "Clinical Disorders of the Heart Beat," Cowan's⁷ "Diseases of the Heart," McKenzie's⁸ "Diseases of the Heart," and Osler and McCrae's⁹ most recent edition of "Modern Medicine."

Auricular flutter is looked on as a regular rapid action of the auricles, in which the origin of the auricular beats is from some point in the auricle other than the normal one in the sinus node. The justification for considering the beat ectopic in origin lies in the fact that

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1 McWilliam, J. A. Fibrillary Contraction of the Heart, *Jour. Physiol.*, 1887, viii, 296.

2 Hertz, A. F., and Goodhart, G. W. The Speed-Limit of the Human Heart, *Quart. Jour. Med.*, 1908-1909, ii, 213.

3 Jolly, W. A., and Ritchie, W. T. Auricular Flutter and Fibrillation, *Heart*, 1910-1911, ii, 177.

4 Lewis, Thomas. Observations upon a Curious and not Uncommon Form of Extreme Acceleration of the Auricle, "Auricular Flutter," *Heart*, 1912, iv, 171.

5 Ritchie, W. T. Auricular Flutter, Edinburgh and London, W. Green & Son, 1914.

6 Lewis, Thomas. Clinical Disorders of the Heart Beat, New York, P. B. Hoeber, 1914.

7 Cowan, J. Diseases of the Heart, Philadelphia, Lea & Febiger, 1914.

8 McKenzie, James. Diseases of the Heart, London, Frowde and Hodder, and Stoughton, Ed. 3, 1914.

9 Osler and McCrae. Modern Medicine, Philadelphia, Lea & Febiger, 1915.

the P wave in the electrocardiograms is abnormal in form. Usually there is some degree of heart block present, but not always. As a rule the ratio between the auricular and ventricular contractions is an even one 2:1, 4:1, or 6:1. Occasionally the ratio is 3 or 5 to 1. The ratio may vary considerably in the same case at different times. The diagnosis is made most easily by means of the electrocardiograph,



Fig 1—Roentgenogram of chest taken Oct 21, 1914, during an attack of flutter

but may be made by the polygraph or even by a radial tracing alone, if changes in the ratio of heart block are caught. For as Fulton¹⁰ has emphasized in a recent paper, although the ventricular rate may be irregular, definite time relations will be met, if groups of ventricular beats are taken which are supposed to correspond to the same number of auricular beats.

¹⁰ Fulton, F. T. "Auricular Flutter," with Report of Two Cases, *THE ARCHIVES INT. MED.*, 1913, xii, 475.

This condition of flutter of the auricles is not influenced by the methods, supposed to stimulate the vagus, which are sometimes successful in stopping an attack of tachycardia. After the administration of digitalis the ratio between the auricular and ventricular rates usually increases, then either fibrillation of the auricles or a combination of

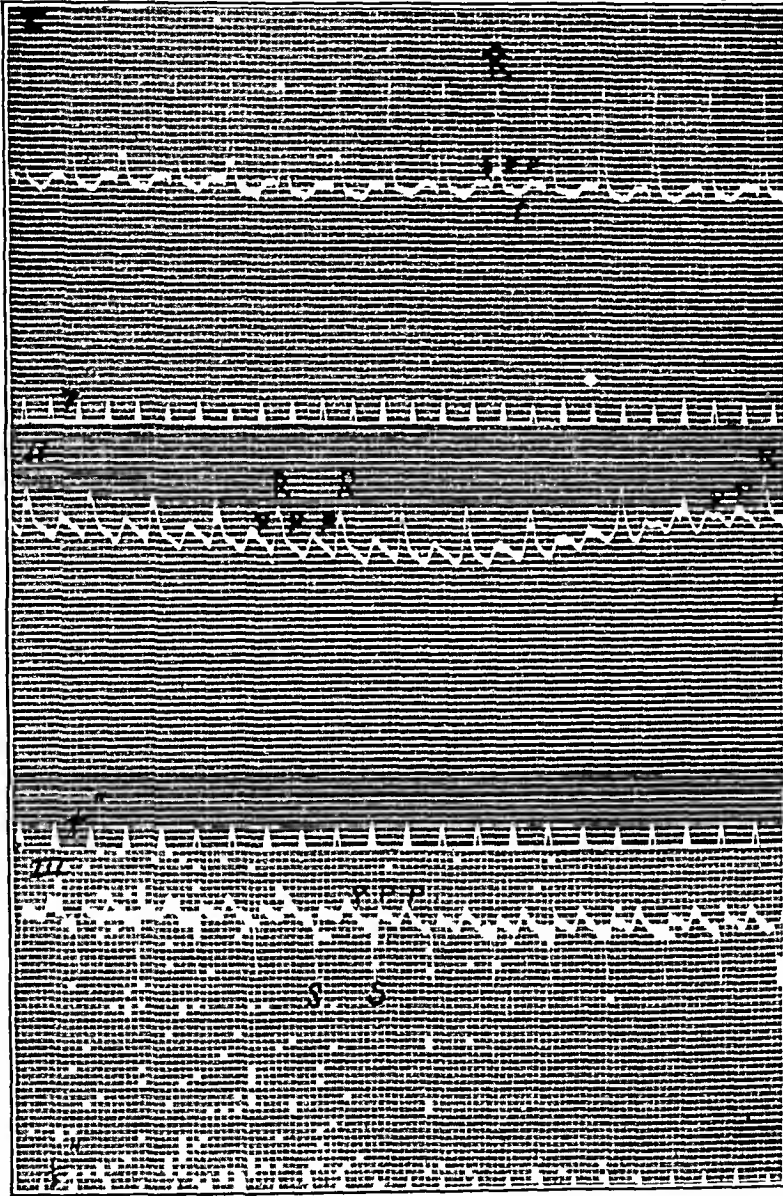


Fig 2—Electrocardiograms taken Oct 22, 1914, of all three leads. They show auricular flutter with a 2:1 heart block and left ventricular hypertrophy. At the end of Lead 2 a break in the 2:1 rhythm is seen.

fibrillation and flutter occurs, and finally the heart returns to its normal rhythm in most cases. Digitalis should be omitted after fibrillation begins.

In many of the cases of flutter reported, more than one attack has been observed. The attacks may last from a few moments to years.

It occurs apparently at any age and associated with a variety of clinical conditions. The symptoms accompanying flutter are not always constant. Probably they are so slight in some cases that the condition passes unobserved. No constant pathologic lesion has been found in the cases that have come to necropsy, but diffuse degeneration of the auricular musculature or involvement of the sino-auricular and auriculo-ventricular nodes has been met.

Although auricular flutter is now well recognized there are many points of practical and scientific interest in regard to this condition which are as yet unsettled. One question of interest is whether the P wave in the electrocardiogram is elevated or depressed in the different leads. The relation between this abnormal rhythm and organic lesion of the heart is still undecided and will remain so until much more necropsy material has been studied. In many of the cases reported the flutter has occurred in hearts in which disease of the mitral valve existed. Is the condition due to one special lesion of the auricles or nerves, or may it be associated with a variety of cardiac lesions? Reports on Roentgen-ray studies during and after an attack are rare, as are also studies on the pulse pressure during the attacks.

During the past winter a case of auricular flutter was under observation in the medical outdoor department and wards of the Peter Bent Brigham Hospital. The study of this case has brought out several points of interest in regard to auricular flutter, and therefore it seems advisable to report it. The following summary of the case is obtained from the records of the outdoor department, the ward records, and notes made by one or the other of us.

The patient, an unmarried Bulgarian, aged 35 (hospital medical number, 1791), entered the hospital Oct 20, 1914, complaining of stomach trouble and shortness of breath.

The family history was unimportant. His past history revealed that at the age of 17 he had tonsillitis for one month. At the age of 18 he had a septic finger with an extension of the inflammation up the arm. At the age of 33 he had another attack of tonsillitis with slight stiffness in the elbow suggesting rheumatism. No history of other diseases, even the ordinary ones of childhood, could be obtained. He had never suffered from shortness of breath before. He fought through the Balkan war in 1913. All venereal disease was denied. He did not use alcohol, drugs, or tea. Formerly he had used considerable coffee but not for some years. Tobacco was limited to one cigar a day.

Twelve days before entrance, the patient noticed rheumatic pains in his shoulders and arms due, he thought, to working in a cold cellar on the preceding day, after taking a hot bath. The pain was not severe enough to stop his work. On the following day he noticed a peculiar feeling about his heart. He could feel the heart strike forcibly against his ribs with some discomfort, but no actual pain. He noticed that the action of his heart was irregular. Six days before entrance he found that he became slightly short of breath on exertion. This increased somewhat up to the time of entrance into the hospital. Otherwise he felt well and was able to lie flat in bed without discomfort.

Physical examination revealed an unusually well-developed short man with good color and rugged appearance. The head, eyes, ears, and nose were normal. The teeth were in good condition, and the throat negative. Except for rapid pulsations, the neck showed nothing abnormal. The lymph glands of the body were not enlarged. The lungs presented no abnormal signs. The abdomen was soft and free from masses. The liver and spleen were not felt. No edema was

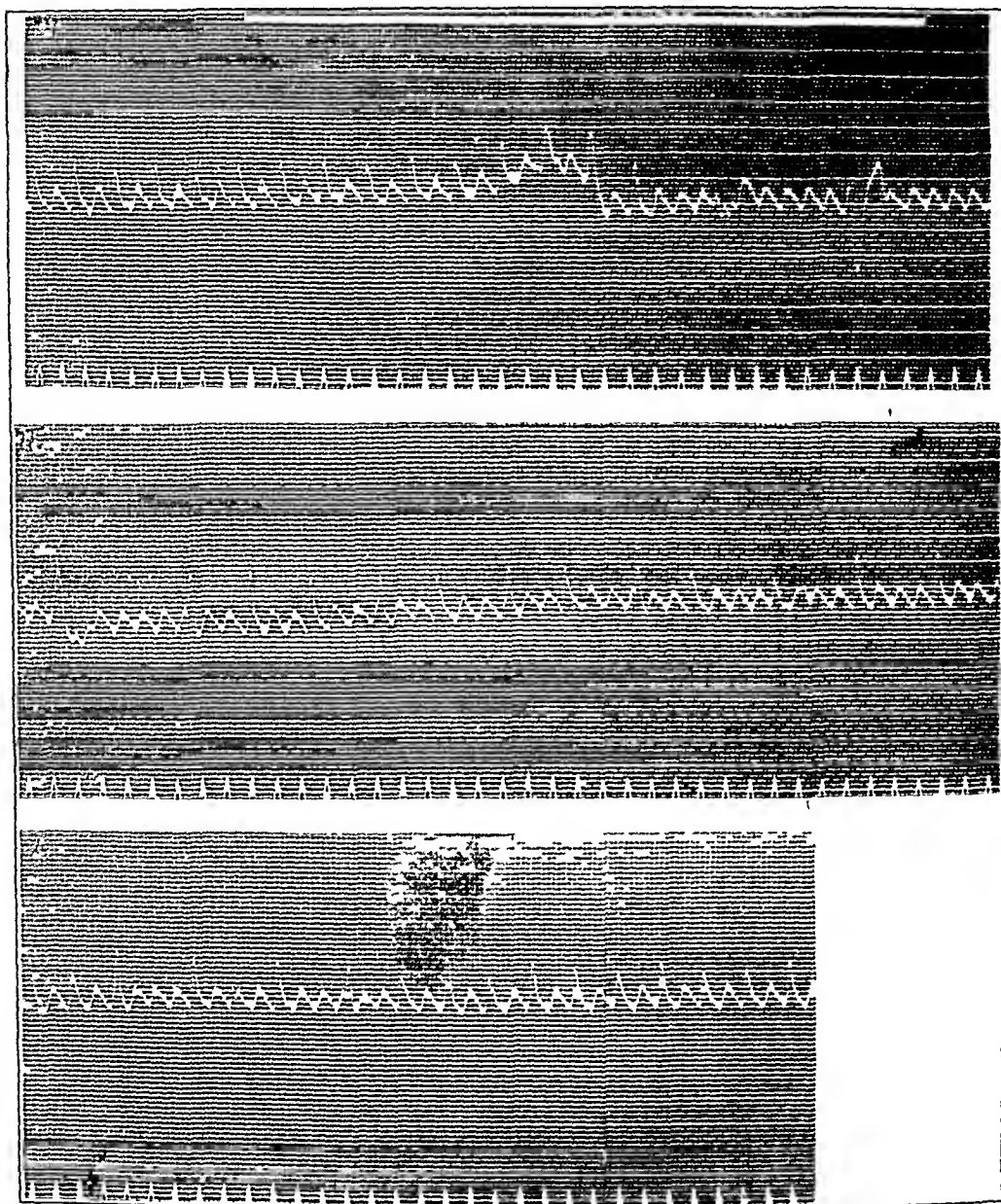


Fig 3—Lead 2, Oct 20, 1914. The three strips represent a continuous tracing. Signal at top marks the duration of left ocular pressure. Marked inhibition of the ventricles occurs and extra systoles appear.

present in the extremities and the reflexes were normal. The peripheral vessels were not rigid or tortuous.

When the heart was examined the apex was seen to be beating rapidly. The point of maximum impulse was in the fifth space, 12 cm to the left of the mid-sternal line. The left border was 13 cm to the left of the mid-sternal line in the sixth space and the right border was 3 cm to the right of the mid-sternal

line in the fourth space. The heart was beating regularly and at the rate of 176 per minute. No thrills were felt. Auscultation revealed a faint systolic murmur at the apex following the first sound. The murmur was followed by a second sound. This murmur was heard all over the precordia and became louder and rougher on approaching the aortic area. No other abnormal heart sounds were heard. The blood pressure by the house officer was 104 systolic and 60 diastolic.

The blood examination, including the Wassermann reaction, was negative. The urine showed a specific gravity of 1.026, a slight trace of albumin, no sugar, an occasional granular cast and pus cell, but no blood.

The report of the Roentgenologist¹¹ on examination of the patient at this time by fluoroscope and roentgenogram states that there is a diffuse dilatation in the region of the descending aorta. Rapid pulsations were seen in this area. The right side of the heart was slightly increased in size, especially in the region of the right auricle. The entire right side of the chest was hazy in comparison to the left. Figure 1 shows the position of the heart and its size during an attack of flutter.

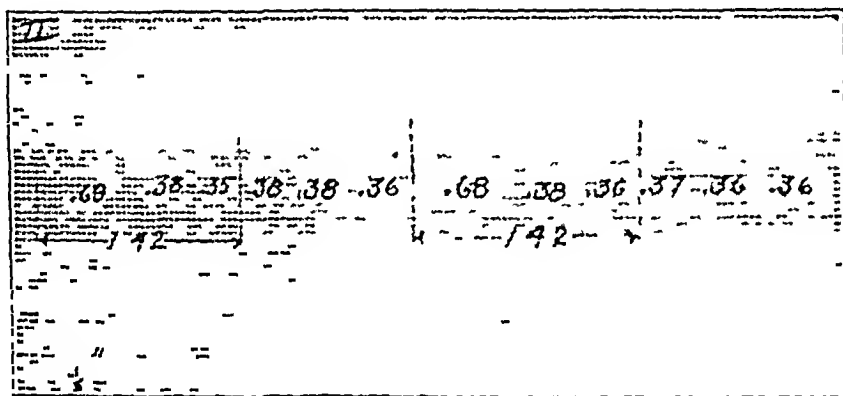


Fig 4—Lead 2, Oct 27, 1914. This shows the increase in degree of auriculo-ventricular block following digitalis, also the grouping of the ventricular beats.

Electrocardiographic study at this time showed an auricular flutter with a fairly constant auriculoventricular 2:1 rhythm. The auricles were beating 342.8 times per minute, and the ventricles 171.4 times. The electrocardiograms also presented evidence of left ventricular hypertrophy, as may be seen in Figure 2. Lead 1 (from right to left arm) in Figure 2 shows a steep initial ventricular complex marked R and a slight negative T wave as the final ventricular deflection. Just before R there is a slight elevation, probably the P wave, due to auricular disturbance. Lead 2 (from right arm to left leg) in Figure 2 shows the triangular form of the P waves so characteristic of flutter. The ventricular complexes are complicated by the superimposed P waves, thus modifying the R and T deflections. Toward the end of this tracing the ventricles break their rhythm while the auricular complexes continue regularly. The electrocardiogram here shows that the auricles have been beating twice as rapidly as the ventricles. Lead 3 (from left arm to left leg) in Figure 2 shows a deep S wave as the initial ventricular deflection, which together with the prominent R wave in Lead 1, denotes left ventricular hypertrophy. There is slight notching in the downstroke of the auricular complex.

In order to bring out more clearly the rapid auricular rate, vagal pressure was tried with the hope of inhibiting the ventricles, but without success. As

11 For the roentgenograms we are indebted to Dr. G. L. Carr.

Levine¹² has shown that the oculocardiac reflex which was first described by Aschner,¹³ is more effective than direct pressure on the vagi in causing vagal inhibition, pressure was applied to the left eyeball of this patient for five and five-tenths seconds. Although it did not have any appreciable effect on the auricular rate, it did cause an inhibition of ventricular contractions after a latent period of three seconds. The electrocardiogram (Fig 3) at this time therefore shows more clearly than those in Figure 2, that the auricles are contracting regularly at a rate of about 340 per minute.



Fig 5—Roentgenogram of chest taken Oct 29, 1914, during normal rhythm

In Figure 3 it is seen that twenty-five successive auricular beats following the beginning of the inhibition failed to produce a normal ventricular contraction. During that time three ventricular complexes appear, each different from the other and from the normal, which show that they started from different foci in the ventricles. Two seconds after the release of ocular pressure, a 3:1

12 Levine, S. A. The Oculo-Cardiac Reflex. An Electrocardiographic Study with Special Reference to the Difference Between Right and Left Vagal and Ocular Pressure in Tabetics and Non-Tabetics, *THE ARCHIVES INT. MED.*, 1915, *v*, Part 1, p. 758.

13 Aschner, B. Ueber einen bisher noch nicht beschriebenen Reflex vom Auge auf Kreislauf und Atmung. *Wien klin. Wchnschr.*, 1908, *xiv*, 1529.

auriculoventricular rhythm was started and twelve seconds after the release of pressure the rhythm returned to the 2:1 ratio which existed before the pressure was instituted.

Pressure on the right eyeball for eight and five-tenths seconds produced inhibition of the ventricle after a latent period of three seconds, which lasted over 43 auricular beats. During this time there were seen seven ectopic ventricular complexes, some of which varied in form from each other. From these different observations and examinations the diagnosis of auricular flutter was made, and some organic disease of the heart was suspected.

The patient felt so well that he refused to stay in the hospital another night, but agreed to come in for daily observation. Digitalis 0.1 gm, three times a day, was begun on October 24, the first day he returned to the out-door department after leaving the hospital. On the 27th, when he had taken in all 1 gm of the digitalis leaves, the electrocardiogram showed an increase in the degree of heart block (Fig 4).

From Figure 4 it is clear that the number of ventricular beats in relation to the auricular systoles varies from a 2:1 ratio to a 4:1 ratio. This electrocardiogram demonstrates the point mentioned above that the ventricular beats, although irregular in rhythm, show a definite time relation to each other if taken in groups corresponding to an equal number of auricular contractions. Thus in this curve it is seen that two sets of ventricular beats in different parts of the tracing although irregular in rhythm, but each corresponding to eight auricular beats, are equal in length. This is peculiar to flutter in contrast with other forms of irregularity with rapid rate. It is also evident that there is a slight variation in the size of the ventricular deflection which suggests *pulsus alternans*. This is especially pronounced after an extra long pause in the ventricular complexes, denoting a condition similar to the *pulsus alternans* seen in some cases following extra ventricular systoles. The *pulsus alternans* observed during flutter with rapid ventricular rate is not considered of so much prognostic value as that occurring in slowly beating hearts.

When he came under observation on October 29, two days later, having had, in all 1.5 gm of digitalis, his heart action was slow and regular. In this patient, therefore, the intermediary stage of auricular fibrillation which usually occurs between flutter and normal rhythm was not observed.

Examination at this time showed the cardiac boundaries 14 cm (12.5 cm tangentially) to the left of the midsternal line in the sixth space, and 4 cm to the right of the midsternal line in the fourth space. A systolic thrill, which was not made out during flutter, was now palpable over the precordia and the neck, most distinctly in the second interspace to the right of the sternum. On auscultation a rough systolic murmur was heard over the whole precordia, loudest in the aortic area, and transmitted to the vessel of the neck. A faint diastolic murmur was heard following the second sound in the aortic area and faintly over the precordia. No pistol-shot sound was heard in the femoral arteries.

The roentgenogram (Fig 5) taken at this time showed no change in the size or shape of the heart from its appearance during the attack of flutter. The electrocardiogram (Fig 6) showed a regular slow auricular rhythm of about 75 per minute. As a rule a normal ventricular complex followed the auricular beat after a slightly prolonged interval, showing a delayed conduction time, possibly due to digitalis. Also there was noted in the electrocardiogram, extra ventricular systoles starting from some ectopic focus. These premature systoles occurred so near the time for the regular beat that they came after the P wave in the electrocardiogram in most cases. The variation from the normal rhythm was so slight that it was not detected in palpating the radial pulse.

These examinations show that the organic heart disease suspected during the attack of flutter consists in a lesion of the aortic valve causing stenosis and slight regurgitation.

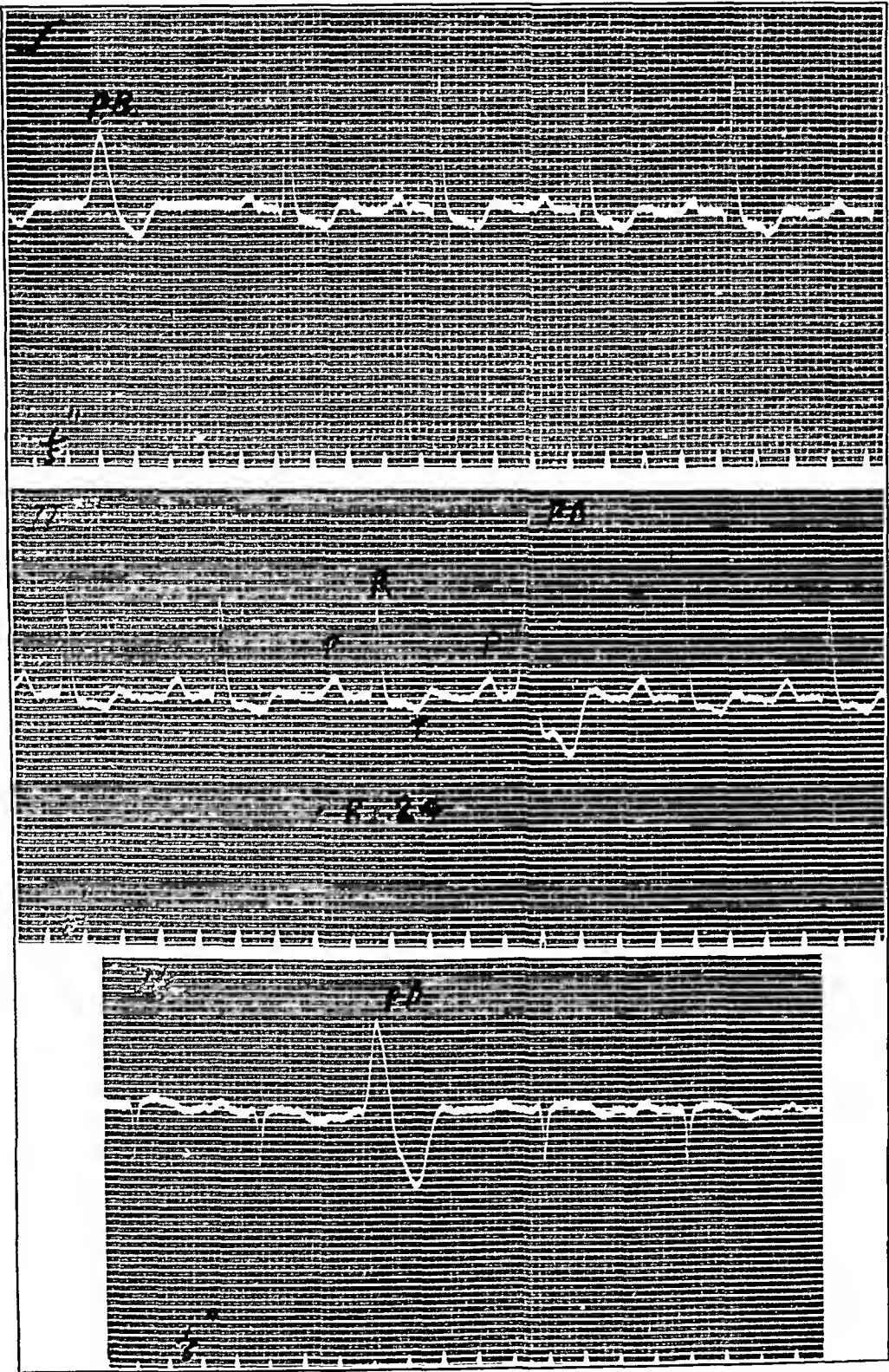


Fig 6—Electrocardiograms taken Oct 29, 1914, of all three leads It shows normal rhythm with extra ventricular systoles (marked P B) and a delayed conduction time (P-R interval 0.24 second)

From October 29 to February 5 the patient was observed occasionally and he reported that at times he was taking digitalis. No reliable information in regard to the digitalis was obtained. On February 5 the patient was found to have another attack of flutter. He stated that in the afternoon of February 2 his heart started to beat rapidly. At that time he had pain in the left ankle and both shoulders. When seen on the 5th his temperature was 99.4 F. Physical examination, fluoroscopic study, and roentgenograms showed no change from the former attack of flutter. Blood pressure observations at this time showed an average systolic pressure of 92 mm of mercury and a diastolic pressure of 80. Tracings from the jugular vein and brachial artery were recorded simultaneously with the electrocardiograms as shown in Figure 7 demonstrating an auricular rate of 336 per minute and a ventricular of 168, a definite 2:1 rhythm. The triangular appearance of the P wave in Lead 2 is again evident with the notch in the down stroke of the P wave, as mentioned above. In the brachial tracing the alternating character of the pulse observed in the ventricular complexes of Figure 4 is seen. In the jugular tracing the "a" and "c" waves are evident but not the "v" waves.

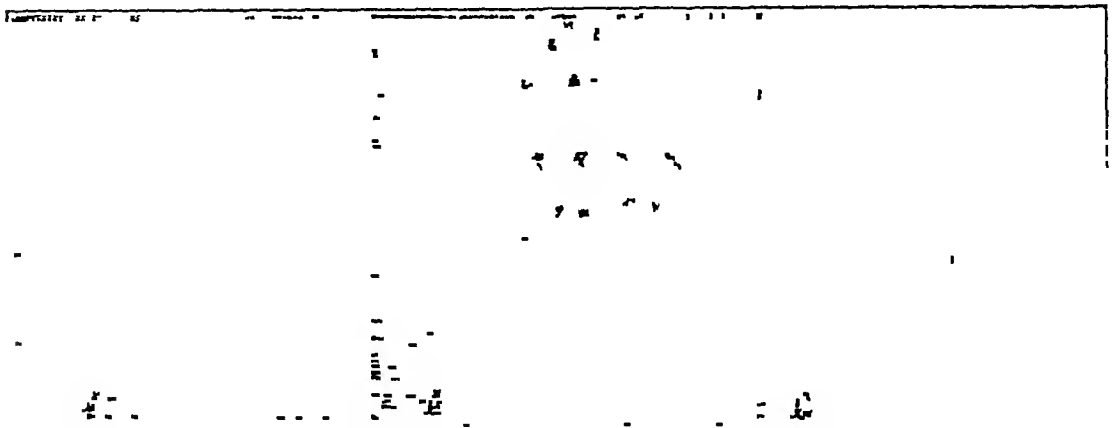


Fig 7—Jugular and brachial tracings taken simultaneously with the electrocardiograms on Feb 5, 1915. Jugular above and brachial tracing below the electrocardiogram. They show auricular flutter with a 2:1 heart block. Alternation of the ventricle is evident in the brachial and electrical tracings. (The flat top in the brachial tracing of Lead 1 is due to a mechanical artifact.)

At this time salicylates were given and also digitalis. After he had taken 0.3 gm of digitalis leaves he noticed at 3 p. m. that his heart became slower and jumping. This condition persisted until he went to sleep at 9 p. m. At 4 a. m. the next morning he awoke with his heart apparently normal.

The accompanying electrocardiogram (Fig 8) shows the three leads taken that day with the heart beating normally. The rate is about 100. The interesting feature is the prolonged P-R interval which denotes a delay in the conduction of the impulse from auricle to ventricle. This interval is 0.25 second which is above the upper limit of the normal. This of course may be due to the digitalis which he had been taking and therefore no conclusions can be drawn from it.

Blood-pressure observations were made at this time. An average of several readings showed that the systolic pressure was 90 mm of mercury, the diastolic 69, making the pulse pressure 21. These readings showed that during the attack of flutter the pulse pressure diminished. Table 1 gives the blood pressure observations during flutter and during normal rhythm. The patient soon afterward dropped out of sight and was reported to have gone back to Bulgaria.

Other points of interest in regard to auricular flutter were brought out at different times in this study. In paroxysmal tachycardia the auricles are apparently under the influence, to some extent, of the vagus. In flutter, however, the auricles are supposed to be very little influenced, if at all, by the methods that are thought to call forth stimulation of the vagus. In this case it has been shown above that ocular pressure inhibited the ventricles. This and such other methods of affecting the vagus, as drinking iced water, pressure on the vagus in the neck, and deep breathing, varied in their action on the auricular rate. No effect was obtained from drinking iced water. By some of the other methods slight but not constant variations in the auricular rate were obtained. In deep breathing a slight but constant slowing of the auricles occurred. This seemed worthy of mention, because normally in flutter, for long periods, the rate for groups of ten beats does not vary more than one or two hundredths of a second. During or



Fig 8—Electrocardiogram taken Feb 6, 1915. It shows normal rhythm with delayed conduction time (P-R interval 0.25 second)

just after deep breathing the rate slowed from 348.8 to 338.3 per minute, or a variation of four or five hundredths of a second in consecutive groups of ten beats. Table 2 shows how constant the time relations are normally for groups of ten auricular beats and the slight but definite slowing produced by the deep breathing. Thus it seems probable that the vagus still has some slight control of the auricles in flutter.

It has been noted that the duration of the electrical disturbance created by the auricular contraction in flutter is relatively long in Leads 2 and 3. It is seen in Figure 3 when the ventricles were inhibited, that this auricular action is so prolonged that one P wave runs up to the beginning of the next, that is, there is a continuous change in the electrical potential. There has been considerable discussion as to the nature of the P wave in flutter in Leads 2 and 3. Ritchie⁵ in his book

speaks of the P wave as upright and often diphasic Lewis⁶ says they are probably upright

By means of the simultaneous venous tracings and electrocardiograms it was thought some light might be thrown on this point Lewis has calculated that normally there is a P-a interval of about eight hundredths of a second between the beginning of the P wave in the electrocardiogram and the start of the "a" wave in the neck Assuming that the P-a interval in flutter was the same as in normal conditions, we measured back in Figure 7 eight hundredths of a second from the

TABLE 1—BLOOD PRESSURE OBSERVATIONS *

During flutter, Feb 5	94 84-10	96 82-14	96-82 14	90 74 16	92-78-14	88-78-10	Aver 92 80 12
During normal rhythm Feb 6	90 72-18	90 70 20	90 65-25				Aver 90 69 21

* The three figures are the systolic, diastolic and pulse pressures respectively

TABLE 2—DURATION IN SECONDS OF GROUPS OF TEN AURICULAR BEATS TAKEN CONSECUTIVELY

Normal, Oct 20, a m	1 74 1 73 1 74 1 74 1 71 1 74
Normal, Oct 20, p m	1 70 1 72 1 71 1 70 1 70 1 70 1 70
Normal, Oct 22, p m	1 74 1 74 1 74 1 74 1 75 1 75 1 75 1 75 1 73 1 74
Held deep inspiration, Oct 20, a m	1 73 * 1 77 1 78 1 78 1 78 * 1 72 1 74 1 73 1 73 1 71
Held deep inspiration, Feb 5, a m	1 79 * 1 80 1 81 1 80 1 80 1 82 1 82 * 1 83 1 83 1 81 1 80

* Deep inspiration held by the patient, resulting in more marked variation than in the normal

TABLE 3—AMPLITUDE OF THE RESPECTIVE WAVES IN MILLIVOLTS *

	Lead I				Lead II				Lead III				P-R	R-T
	P	R	S	T	P	R	S	T	P	R	S	T		
Flutter	0.05	1.8	—	-0.2	-0.35 +0.35	1.2	—	?	-0.25 +0.25	0.1	1.2	?	0.26	0.21
Normal rhythm	0.3	2.0	—	-0.4	0.4	1.1	—	0.1	0.1	0.1	1.6	0.3	0.25	0.28

* The P-R and R-T times are measured in seconds as represented by the figures in Leads 1, 2 and 3

beginning of the "a" wave in the jugular tracing and found that the point came at the notch on the down stroke of what was supposed to be the P wave Of course the question may be raised as to whether the point from which we measured was the beginning of the "a" wave Our feeling that such was the case was increased on examination of another electrocardiogram in Lead 2, in which, due to a break from 2 1 to a 4 1 rhythm, there was no doubt in regard to a certain wave being an "a" wave By measuring back eight hundredths of a second

in this tracing the notch in what has been called the down stroke of the P wave was again met. It seemed more reasonable therefore to call this point the beginning of the P wave, to consider the wave diphasic, and to look on the notch as the junction between the preceding P wave and the beginning of the next one. However, another weak point in this contention is that it is not perfectly established that the beginning of the P wave in flutter occurs eight hundredths of a second before the beginning of the "a" wave in the jugular, as it does normally.

A study was also made of the height of the waves in the different leads and the length of the P-R interval and the R-T interval during an attack of flutter and when the heart was in normal rhythm. These results are summarized in Table 3. In all three leads it will be seen that the amplitude of the R and S waves are only slightly changed from the normal during flutter. In Lead 1 the T wave is slightly higher during the normal rhythm. In Leads 2 and 3 no conclusion can be reached with regard to the T waves, because their form was obscured by the superimposed P waves. In Lead 1 the P wave is much diminished in height during flutter, while in Leads 2 and 3 the total of the up and down deflections of the P wave shows a marked increase over the normal. Each up or down deflection, however, was nearly equal to the height of the normal P wave. The P-R interval remained the same during the attacks as when the heart was beating in normal rhythm, but the R-T time showed considerable diminution during the flutter.

SUMMARY

Auricular flutter was observed twice in a man with organic disease of the aortic valve consisting in stenosis and slight regurgitation. Opportunity was given to study him during and between attacks by means of the electrocardiograph and also by tracings from the jugular vein and brachial artery, taken simultaneously with the electrocardiogram.

In this man the auricular rate during flutter varied at different times from 350.5 per minute to 324.7 per minute. The ventricles were beating most of the time during the attacks at half that rate showing a 2:1 block.

During the attack of flutter the auricles were practically independent of vagus control, although a slight effect on the auricular rate could be produced by deep breathing. The ventricles could be inhibited by pressure on either the right or left eye, but the auricles could not be inhibited. During the attack of flutter there was slight pulsus alternans as shown in both the electrocardiogram and brachial tracings. This

disappeared when the heart returned to its normal rhythm. The amplitude of the T wave was diminished in Lead 1, the duration of the ventricular cycle (R-T interval) was shortened, and in Leads 2 and 3 the P waves were much increased in amplitude.

Roentgenograms showed no appreciable difference in the outline of the heart during the attack, and the pulse pressure, which was small normally in this case, diminished during flutter. In this case of flutter the P wave in Leads 2 and 3 is probably diphasic and the notch on the downstroke of the auricular complex is the junction between two P waves.

SINO-AURICULAR HEART BLOCK

WITH REPORT OF A CASE IN MAN *

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While abnormalities in conduction and partial or complete blocking of the cardiac impulse at the auriculoventricular junction is a fairly frequent clinical condition, similar disturbances at the sino-auricular junction are apparently exceedingly infrequent in the higher animals and in man. So far as we have been able to find, only four clinical cases in which the diagnosis was satisfactory have been reported. The first case was reported by Mackenzie¹ in 1902, in a patient during an attack of influenza. The second case was reported by Wenckebach² in 1906, in a man, aged 30, who was apparently normal aside from the disturbance in the heart rhythm. The third case, described by Hewlett³ in 1907 and the fourth by Rihl⁴ in 1908 were in cases of advanced cardiac and arterial disease.

In all of these the diagnosis was made by the aid of the venous pulse and rests on the dropping of "a" waves in an otherwise regular auricular rhythm. In all, the sino-auricular block was associated with auriculoventricular block. In Mackenzie's case the dropping of auricular beats occurred during complete auriculoventricular block, while in Wenckebach's case each dropped auricular systole was always preceded by a dropped ventricular beat. Hewlett's and Rihl's cases were associated with partial auriculoventricular block, and in the latter the dropped auricular cycle frequently followed a blocked ventricular cycle as in Wenckebach's case. In these two cases the sino-auricular block was noted only after the administration of digitalis. Mackenzie ascribes the condition in his case to the toxemia. Wenckebach's case was in an apparently normal man who came to the clinic only for research purposes. No statement of clinical examination other than the interpretation of the jugular curves is given. Hewlett's case was in a 44 year old alcoholic with pleuritic adhesions, arteriosclerosis and

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1 Mackenzie Brit Med Jour, 1902, ii, 1911

2 Wenckebach Arch f Anat u Physiol, 1906, p 297

3 Hewlett, Albion Walter Digitalis Heart Block, Jour Am Med Assn, 1907, xlviii, 47

4 Rihl Deutsch Arch f klin Med, 1908, xciv, 286

liver cirrhosis Rihl's case was in a woman, aged 63, who showed valvular lesions and advanced arteriosclerosis

Two cases, described by Joachim⁵ in 1905, and one case described by Danielopolu⁶ in 1913, were probably not sino-auricular but auriculo-ventricular block, since "a" waves apparently occur between the normal beats on the venous pulse curves published in these articles. The curves in each case are very difficult to interpret because of the exceedingly weak pulsations shown.

Since the activity of the auricle is the first feature of the cardiac contraction which finds expression in the venous pulse curve or electrocardiograph in man,⁷ the only criterion of sino-auricular block

5 Joachim *Deutsch Arch f klin Med*, 1905, xcv, 373

6 Danielopolu *Arch d Mal du Coeur, des Vaissaux et du Sang*, 1913, vi, 792

7 Gibson (*The Practitioner*, 1907, lxxviii, 589) described a wave on the venous pulse in a clinical case which he designated as the "s" wave and ascribed to contraction of the musculature of the vena cava preceding the auricular contraction. This is probably the same wave described by Hirschfelder (*Bull Johns Hopkins Hosp*, 1907, xviii, 265) under the designation "h" and ascribed by him to temporary closure of the tricuspid valve in mid-diastole at the end of the period of most rapid ventricular filling. Eyster (*Jour Exper Med*, 1910, xii, 257) showed that this wave was a normal event of the venous pulse record in slow heart rate and was evidently from its position in cycles of varying length, a diastolic and not a presystolic event. He further showed that in the dog no wave occurred on the venous pulse that could be ascribed to contraction of the mouths of the superior vena cava even when an extra systole was initiated by stimulation of this region. A wave on the venous pulse curve ("x" wave) described by Eyster (see above) following the "h" wave in slow heart rates was apparently also a diastolic feature and unassociated with any possible contraction of the venous or sinus region of the heart. Subsequent work by Thayer (*Boston Med and Surg Jour*, 1908, clviii, 713) showed the close association of the "h" wave with the so-called shoulder on the volume curve of the mammalian ventricle, the point which marks the end of the period of rapid ventricular filling, and Eyster (*Jour Exper Med*, 1911, xiv, 594) found that it occurred practically coincident with the third heart sound as recorded by the microphone and string galvanometer. These facts tend to confirm the diastolic nature of this wave and to render probable the explanation of its cause advanced by Hirschfelder and Thayer. Rehfish (*Arch f Anat u Physiol*, 1906, Sup, p 152) found on the suspension curves of the auricles, in the exposed heart of the rabbit and dog, a small wave preceding the main movement resulting from auricular systole which he referred to contraction of the sinus region of the heart. The interpretation would seem to be at best exceedingly doubtful.

The region of the heart which recent work has shown as the normal seat of impulse initiation, the sino-auricular node, is closely associated anatomically and physiologically with the right auricle. Electrocardiographic methods have shown that activity in this region normally precedes activity in the right auricle by 0.03 second or less in the dog's heart (Eyster and Meek, *The Interpretation of the Normal Electrocardiogram*, *THE ARCHIVES INT MED*, 1913, xi, 204). This short interval probably explains why the sino-auricular node normally gives no expression on the electrocardiogram separate from the activity ("P" wave) of the auricle. Under certain conditions in which the interval of sino-auricular conduction is probably delayed, the "P" wave of the electro-

which has as yet been applied clinically or experimentally is the absence of certain auricular beats in an otherwise regular auricular rhythm. The failure of the auricle to contract at such times may be due, as Hewlett³ has pointed out, to (1) weakness of its muscle, (2) inadequacy of the stimulus, (3) blocking of the impulse between its point of origin and the auricle. Since in the cases which have been observed the curves show no evidence of any noteworthy variations in the size of auricular beats when these are present, the probability of variations in the strength of the excitation or in the responsive power of the muscle, of sufficient magnitude to account for a complete absence of contraction, would seem to be extremely improbable. That blocking of the stimulus is the true explanation is furthermore rendered probable by certain characteristics which the rhythm presents in common with auriculoventricular block. Of these the most significant are the facts that the intervals between the auricular beats immediately following the intermission is somewhat greater than in subsequent cycles and that the long cycles are nearly always somewhat less than twice the length of the short cycles. In the case of auriculoventricular block the latter feature finds its explanation in the fact that the period of auriculoventricular conduction is unusually long immediately before and unusually short immediately after the blocked cycles.

Several other authors have described cases of supposed sino-auricular block, the diagnosis of which was based on the character of the arterial pulse as counted or recorded. The extreme difficulty of excluding auriculoventricular block or extrasystolic arrhythmia in the absence of venous pulse or electrocardiographic records renders the interpretation in these cases open to serious question. Heincke, Abert, Mueller and von Hoesslin⁸ described a case in which the arrhythmia suggested disturbances in sino-auricular conduction without actual block, and a second case in which the radial pulse suggested a partial sino-auricular block. Riebold⁹ described two cases, which showed changes in pulse rate suggesting sino-auricular block. In one of these the pulse was very slow and no visible jugular pulsations occurred

cardiogram may show a partial division into two waves, as has been described by Hering (*Arch f d ges Physiol*, 1912, cxliv, 1) and Eyster and Meek (see above). Probably the first wave in this case is a true measure of the activity of the seat of impulse formation. Many facts tend to support the view that the sino-auricular node normally does not show any or at best only an exceedingly small contraction. It is in this region where automaticity and conductivity are most developed, probably at the expense of contractility. The first movement of sufficient magnitude to affect the venous pulse does not occur until the right auricle enters into contraction. (Eyster *Jour Exper Med*, 1910, xii, 257) and Eyster and Meek (see above).

8 Heincke, Albert, Mueller and Hoslin. *Deutsch Arch f klin Med*, 1908, xciii, 459.

9 Riebold. *Ztschr f klin Med*, 1911, lxxiii, 1.

during the long pauses Von Hoesslin¹⁰ produced vagus pressure in a cardiac case and obtained dropped radial beats which he interpreted as sino-auricular block

Hering¹¹ in 1901 described the first instance of supposed sino-auricular block obtained experimentally in animals He observed the exposed hearts of rabbits and dogs dying from asphyxia and described varying degrees of partial block between the mouths of the superior vena cava and the right auricle Similar observations were later recorded by Hirschfelder and Eyster¹² Since it is now known that the heart beat normally arises not in the superior vena cava but in the sino-auricular node, and since it has been shown that dying hearts



Fig 1—Interpreted as 2:1 sino-auricular heart block The auricular cycles average 1.83 seconds Figures 1 and 2 were made with Lead I (right and left hands) Figures 3, 4, 6, 7, 8, and 9 are electrocardiograms made with Lead II (right hand and left leg) All records are to be read from left to right The time records in each case record fifth-second intervals

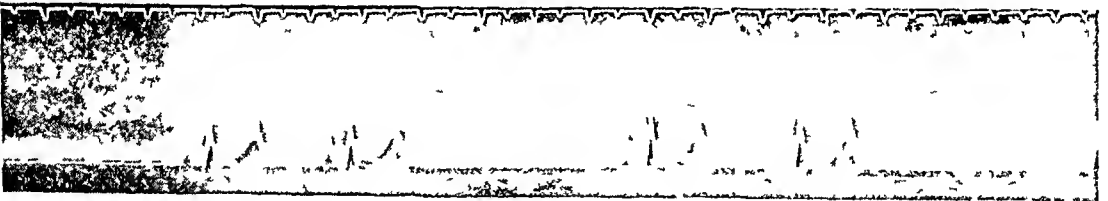


Fig 2—Interpreted as 3:2 sino-auricular block The long cycles average 2.13 seconds, the short cycles 1.03 seconds

may show initial contractions in regions which were not normally nor even at the time the seat of impulse initiation (Eyster and Meek¹³), these observations would seem to have little significance Hering¹⁴ later denied that sino-auricular block could exist in the mammalian heart because of the absence of a separate and independent sinus venosus In 1906, however, he¹⁵ described two cases of apparent sino-auricular block, one in a rabbit, the other in a dog, occurring without

10 Von Hoesslin *Deutsch Arch f klin, Med*, 1914, cxiii, 537

11 Hering *Arch f d ges Physiol*, 1901, lxxxvi, 553

12 Hirschfelder and Eyster *Am Jour Physiol*, 1907, xviii, 222

13 Eyster and Meek *Heart*, 1914, v, 137

14 Hering *Ztsch f exper Path u Therap*, 1906, iii, 511

15 Hering *Ztschr f exper Path u Therap*, 1906, iii, 511



Fig 3—Interpreted at 4 3 sino-auricular block The long cycles average 2 09 seconds, the short cycles 1 37 seconds

known cause during the course of experiments carried out with other purposes in view. The criterion of diagnosis was the same as in the previously reported clinical case of Mackenzie¹. Hering found that the suspension curves of the right auricle of the exposed heart showed occasional dropped beats in an otherwise regular rhythm. In 1907, Erlanger and Blackman¹⁶ described sino-auricular block in excised and artificially perfused rabbits' hearts, resulting apparently from mechanical disturbance (traction) of the region of the sino-auricular node.



Fig 4—Showing alternating periods of sinus rhythm and auriculoventricular rhythm

The criterion for diagnosis was the same as in Hering's experiments, dropped beats in the auricular suspension curve. In one the very slow rate of beat (less than 60 per minute) and the short As-Vs intervals (apparently less than 0.05 second) suggest an auriculoventricular rhythm in which the seat of impulse formation is in the auriculoventricular node at the base of the interauricular septum. In the other example the alternation in the size of the auricular beats suggests the regular occurrence of auricular extrasystoles, an extrasystole following each normal beat and followed by a compensatory pause. Erlanger

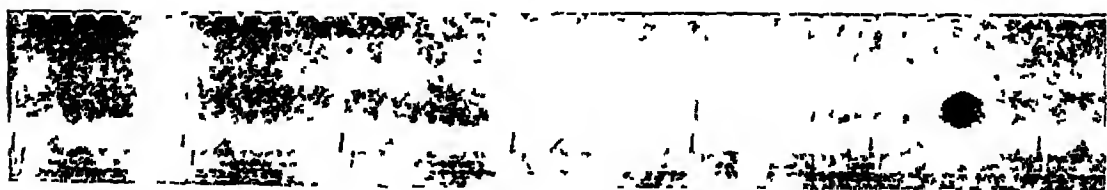


Fig 5—Interpreted as a normal rhythm. Auricular cycles average 1.17 seconds in length

and Blackman were able to obtain the results described in two of six experiments in which traction was made on the sino-auricular node.

Cushny¹⁷ in studying the effect of aconitin on the dog's heart *in situ* noted that not infrequently there was a sudden doubling or halving of the auricular rate and concluded that the condition was the result of the disappearance or appearance of sino-auricular block. Auriculo-

¹⁶ Erlanger and Blackman. *Am Jour Physiol*, 1907, xix, 125

¹⁷ Cushny. *Heart*, 1910, i, 1

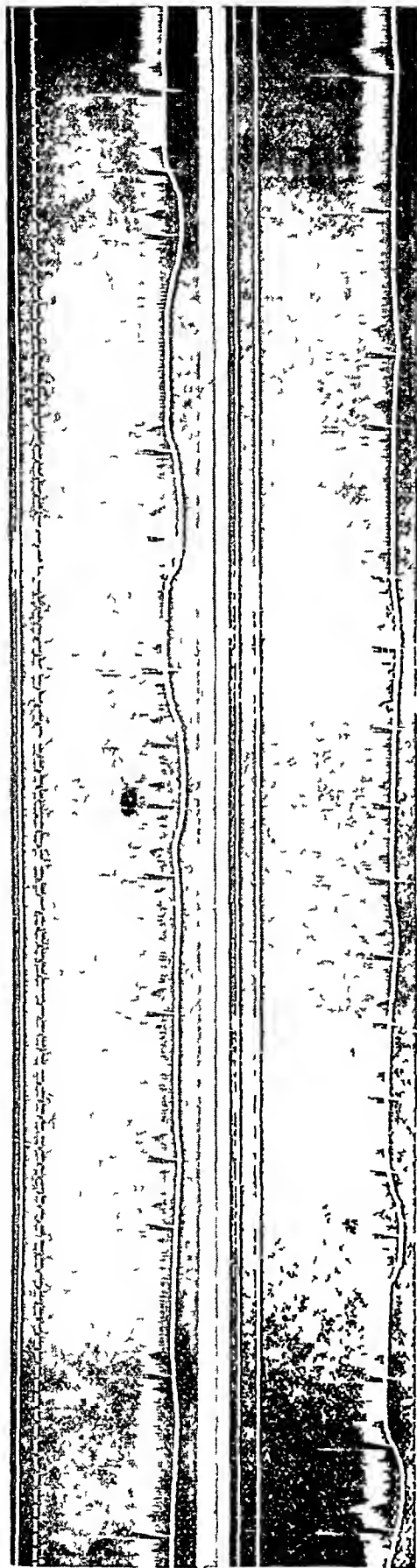


Fig 6—Shows transitory abolition of 2 1 and 3 2 sino-auricular block by deep breathing The lowest line of the records shows the respiratory movements, downstroke representing inspiration The lower record is a direct continuation of the upper and shows the return of block as the respiratory movements become of normal depth



Fig 7—Shows transitory abolition of a 3 2 and 2 1 sino-auricular block by a series of swallowing movements (signalled by line at top of record)

ventricular block, partial or complete, was a very common result of aconitin administration in these experiments

Eyster and Meek,¹⁸ in 1913, investigated the arrhythmia in dogs that follows the administration of large doses of morphin, and concluded from electrocardiographic curves that the cause was a sino-auricular block alone or combined at other times with auriculoventricular block. Large doses of morphin (up to 2 grams) caused a slow regular heart rate which showed arrhythmia during its development or during the stage of recovery from the drug. The condition of slow regular pulse could be removed temporarily at any time by the injection of atropin, and in the change to a fast regular rate of approximately twice or three times the slow rate, marked arrhythmia was present. The results led to the conclusion that the slow regular beat

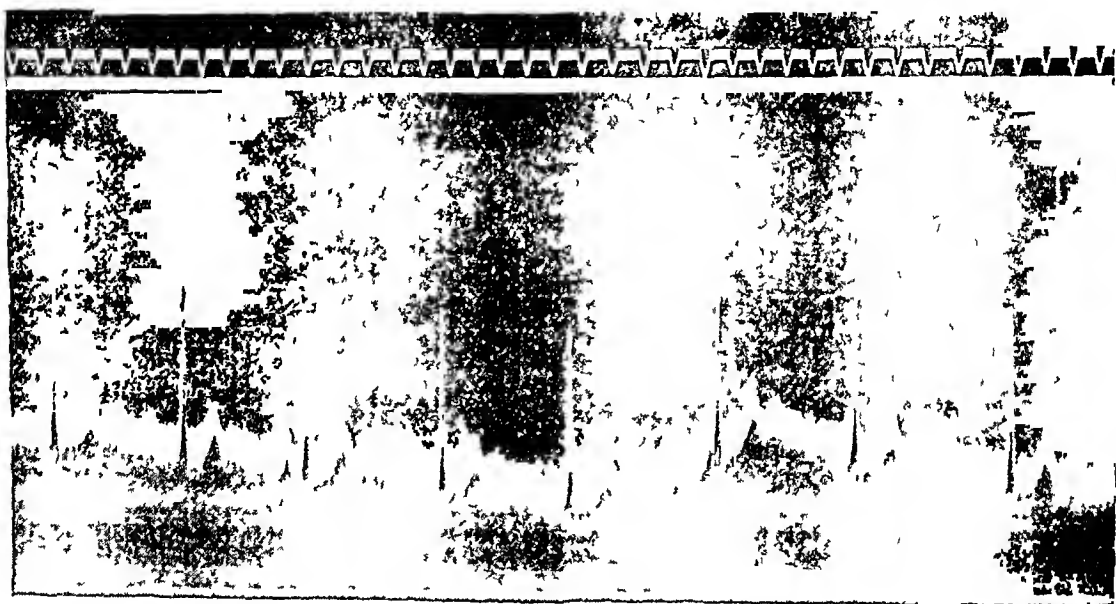


Fig 8—Period of auriculoventricular or "nodal" rhythm following exercise in sitting posture

was a partial sino-auricular block of a regular nature in which, as a rule, every other or two successive sinus impulses were blocked. During the recovery from this slow rhythm, occurring spontaneously as a result of a wearing away of the morphin or resulting from its antagonism by atropin, various stages of partial sino-auricular and auriculoventricular block occurred. That morphin produces the slowing and arrhythmia of the heart by its action on the vagus mechanism, had been previously shown by von Egmond¹⁹ and more recently by Einthoven and Wieringa²⁰ and by Cohn.²¹

18 Eyster and Meek. *Heart*, 1912, iv, 59

19 Von Egmond. *Arch f exper Path u Therap*, 1911, lxxv, 197

20 Einthoven and Wieringa. *Arch f d ges Physiol*, 1913, cxlix, 48

21 Cohn. *Jour Exper Med*, 1913, xviii, 715

REPORT OF A CLINICAL CASE OF SINO-AURICULAR BLOCK

J O R, a university instructor, aged 31, requested examination at the medical clinic because of slow irregular heart. He had been the subject of rather frequent examinations and states that his heart has been slow since early in life when his attention was first called to it by his family physician. He has recently been refused life insurance because of the slow heart rate. Family history is negative. Personal history negative except a severe attack of diphtheria at 2 years of age. Health good except occasional attacks of headache of migraine nature. Physical examination shows a fairly well-nourished man, height 5 feet, 9 $\frac{3}{4}$ inches, weight 143 pounds, and is entirely negative except for a moderate degree of extension of cardiac dulness to the left. No dulness to the right of the sternum. Heart sounds are clear. Pulse irregular, varies at different times from 36 to 60 beats per minute. Blood pressure (auscultatory method) in erect position 110 mm systolic, 75 mm diastolic. Urine negative except an occasional hyaline cast. Roentgenogram shows moderate degree of enlargement of the heart mainly involving the left ventricle.

The subject was examined by the aid of the electrocardiograph and jugular pulse tracings during seven periods of examination extending over ten weeks. Examination of the numerous records made during this time show that the longest heart cycle recorded was of 22 seconds duration, the shortest, except after exercise, 0.87 second. The heart cycles fall with remarkable constancy into two groups, the long cycles averaging about two seconds and the short cycles averaging about one second in length. In rare instances cycle lengths of the long variety as low as 1.6 seconds and short cycles as long as 1.2 seconds were observed. A regular succession of long cycles, a condition observed on several occasions, gave a slow regular heart rate of about thirty beats per minute (Fig 1). A regular succession of short cycles gave a regular heart rate of approximately double this rate. A condition much more frequently met in the records is a rate intermediate between these, usually from thirty-six to forty-eight beats per minute and which is always arrhythmic. This may assume a number of different forms, depending primarily on the presence or absence of a definite relation between the short and long cycles. The relation between the two may be such as to give a bigeminal (Fig 2) or trigeminal pulse (Fig 3), two or three short cycles alternating with one long cycle with perfect regularity over long periods of time. Or the number in each group of short cycles may be much greater and markedly variable, varying from time to time from two to ten or more and frequently interspersed with several long cycles in succession. Finally there may be only an occasional long cycle interposed in a regular series of short cycles and the heart rate approaches the regular fast rate described above.

The long cycles are in nearly all instances approximately double the length of the short cycles, and neither the electrocardiogram nor the venous pulse show any movement during the former which could be interpreted as an auricular beat, the excitation from which is blocked before reaching the ventricle. The absence of "P" waves on the electrocardiogram and of "a" waves on the venous pulse during the long pauses make impossible the interpretation of the condition as auriculoventricular block. We are evidently dealing with a case of "dropped auricular beats in an otherwise regular auricular rhythm," pointing clearly to the interpretation of sino-auricular heart block. It would seem probable that the slow regular rhythm at the rate of about thirty beats per minute is to be interpreted as a regular 2:1 partial sino-auricular block, while the fast regular rhythm at approximately double this rate represents an entirely normal heart beat without interruption in the passage of any excitation from its points of origin to the remainder of the heart. The intermediate rates of beat, which, as noted above, are always arrhythmic, represent varying degrees of partial sino-auricular block. The arrhythmias show certain characteristics which have been noted in the cases of sino-auricular block previously described. The length of

the long cycles is usually slightly less than twice that of the associated short cycles, and the first cycle of each group of short cycles is usually somewhat longer than the remainder

The rate of discharge of impulses from the sino-auricular node, according to the above interpretation, is under usual conditions approximately 60 per minute and is remarkably uniform throughout our observations. The records show no single instance which could be interpreted as representing the blocking of more than one sinus impulse in succession. The longest cycle recorded was 22 seconds. The condition would seem to be represented therefore by a series beginning with a 2 1 partial and regular block, passing through 3 2, 4 3, 5 4 regular partial block, irregular partial block varying from 2 1 to only occasional blocked impulses, and finally a 1 1 normal and regular heart beat

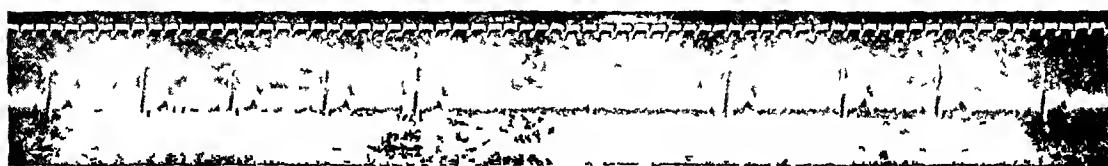


Fig 9—Influence of mechanical pressure on the right vagus nerve

The case would seem to present certain points of unique character which are worthy of comment. The presence of this condition in an active man who is apparently in good health has its only precedent in the case described by Wenckebach². It is the only case of sino-auricular block, so far as we can find, which has been entirely unassociated with auriculoventricular block. The only blocked auricular beats present in our observations occurred during experimental stimulation of the right vagus nerve by compression in the neck as described below. The regular character of the block present at various times on the one hand, and the ease with which the type of block could be varied by relatively slight disturbances (muscular movement, mental distur-

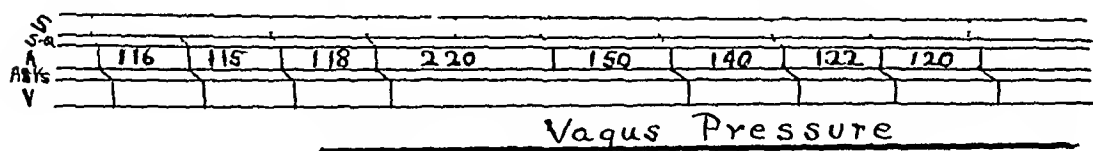


Fig 10—Schematic reproduction of record shown in Figure 9

bance) on the other hand, are features not emphasized in the previously reported cases. Another interesting and unique feature in this case is the occasional occurrence of an auriculoventricular or "nodal rhythm". When in this condition, the electrocardiogram shows a regular succession of cycles with "P" waves fused with or preceding the "R" waves by an abnormally short interval. The change from a condition of sino-auricular block to that of auriculoventricular rhythm was noted in several instances on changing from the lying to the sitting posture. In one instance this change was produced by muscular exercise in the sitting posture. The cycles in auriculoven-

tricular rhythm are longer than the unblocked cycles in the sinus rhythm. The result of the change from sino-auricular block to auriculoventricular rhythm was usually, however, an increase in heart rate per minute. In a few records short periods of auriculoventricular rhythm alternated with periods of sino-auricular rhythm (Fig 4)

In the attempt to find the reason for the existence of this condition in an apparently healthy man without evidence of other cardiac affection, consideration of the ease with which the type of block could be varied by relatively small external changes, of the influence of digitalis in the production of sino-auricular block in the previously reported cases, and especially the experimental production of sino-auricular block in dogs by morphin, led us to investigate the influence of the vagus nerves. That the condition was one easily influenced as to its character was evident from the readiness with which the rate and

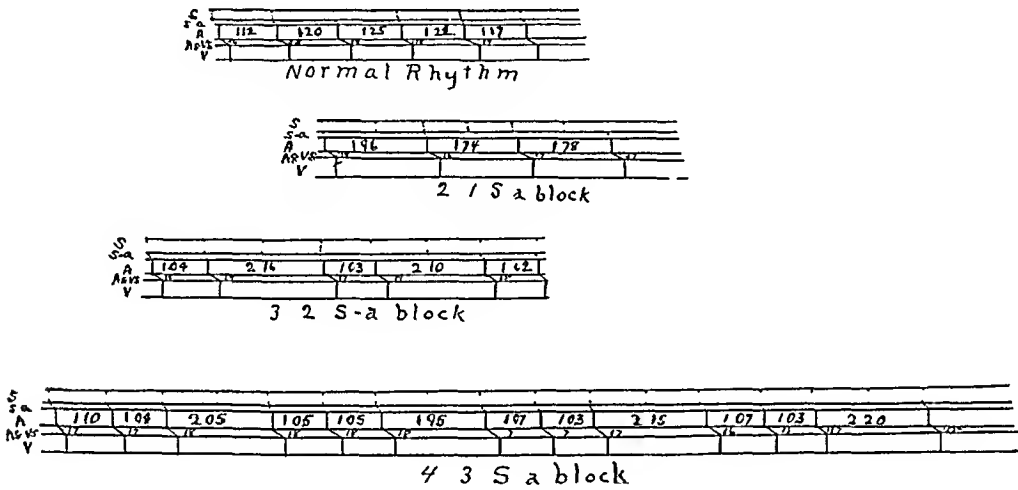


Fig 11—Schematic reconstruction of curves showing normal rhythm and 2 1, 3 2, and 4 3 sino-auricular block

character of the beat changed. Sitting or lying quietly the heart would frequently fall into the slow regular rhythm of approximately 30 beats per minute, while slight muscular movement or disturbance of the quietness of the surroundings would lead to the characteristic arrhythmic faster rates, frequently showing groups of six to ten or even more successive short cycles. Experimentally it is evident that decrease in vagus tone is largely responsible for the moderate changes in heart rate resulting from muscular activity (Gasser and Meek²²), and the changeable character of the beat in the present case suggested some such factor rather than an actual lesion within the conductive system, which would be expected to exert a more constant influence and tend to keep the character of the beat more nearly the same under fairly similar conditions

22 Gasser and Meek. Am Jour Physiol, 1914, xxxiv, 48

The experimental observations that we have made indicate that the vagi are at least in part responsible for the sino-auricular block in this case. The subcutaneous administration of 1.0 mg of atropin completely abolished the block for a time and led to the production of a regular heart rate of approximately 60 beats per minute. Figure 3 shows a trigeminal pulse present immediately before the administration of atropin, Figure 5, the regular beat present nine minutes following the injection. Other records showed that the trigeminal pulse passed, within four minutes following the administration, into a faster rate with only occasional dropped beats. A little later the rhythm became entirely regular at approximately 60 beats per minute, which condition lasted up to eighteen minutes after the injection, when occasional dropped beats were again observed. Within a half hour the condition had returned to practically that present before the atropin administration.

It is well known that normally the heart rate increases during inspiration, due largely at least to inhibition of vagus tone. Respiratory records made simultaneously with the electrocardiogram indicated

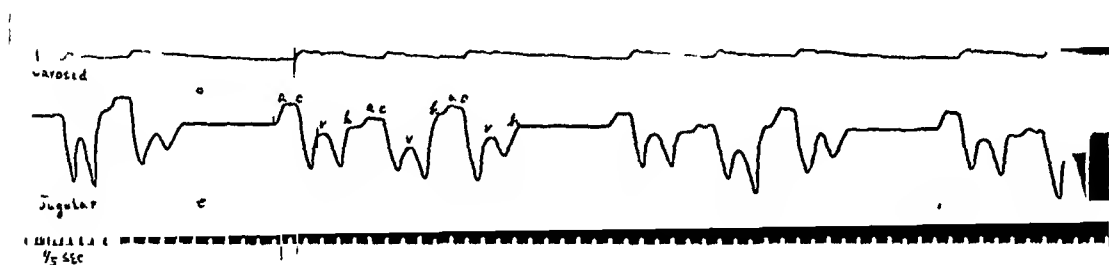


Fig 12—Carotid and jugular tracings showing 4:3 sino-auricular block. The absence of "A" waves in the long cycles excludes auriculoventricular block.

no change in the more regular types of block, such as the 3:2 and 4:3 rhythms, corresponding to the respiratory phase. At times when the type of block was irregular, when groups of short cycles of varying number alternated with long cycles, some relation to the respiratory phases was apparent. The long cycles were nearly always associated with expiration, and inspiration usually, but not always, called forth a group of short cycles. Rapid and deep breathing movements usually abolished the block and called forth a long uninterrupted series of short cycles (Fig 6).

A succession of swallowing movements, a procedure which normally usually leads to a quickened pulse presumably due to diminished vagus tone, was found temporarily to abolish the existing block and to lead to the production of a regular fast rate of beat (Fig 7).

The effect of muscular exercise was usually to remove an existing sino-auricular block and to accelerate slightly the rate of discharge

of the sino-auricular node In one instance the cycle lengths in the unblocked cycles averaged 0.98 second before and 0.8 second immediately after the exercise Arm exercise in the sitting posture in another instance converted a sinus rhythm with short cycle lengths of about 0.93 second and with a 3:2 and 4:3 sino-auricular block, into an auriculoventricular rhythm with cycle lengths of 0.82 second (Fig. 8)



Fig. 13—Carotid and jugular tracing showing transition from 2:1 sinoauricular block to a normal rhythm

Pressure on the right vagus nerve in the neck may cause the block to appear when not previously present (Figs. 9 and 10). Pressure on the left vagus produced merely a slowing of the sinus rate without evidence of block. In the curve reproduced, the sino-auricular block is combined with one blocked auricular beat, the only instance of auriculoventricular block in any of the records obtained.

The experimental results seem to us to point strongly to the vagus mechanism as at least in part responsible for the condition of sino-

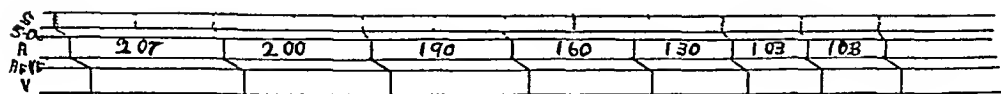


Fig. 14—Schematic reproduction of record reproduced in Figure 13, showing probable interpretation

auricular block in this subject. These factors which are known to inhibit vagus tone (atropin, inspiration, swallowing, exercise), tended to cause a disappearance of the block, while increase of tone of the right vagus produced by mechanical pressure on this nerve may cause the block to appear when not previously present. From the clinical standpoint there is no other apparent factor. The heart, except for the arrhythmia and slow rate and a moderate degree of ventricular

hypertrophy,²³ and the vascular system, are normal. In the absence of any apparent factor other than the vagus mechanism, we are inclined to attribute the condition in this case to an abnormal vagus tone. The influence of the vagus on the conductivity in the heart is evident from the experiments of many investigators on the lower animals and from the work of Ritchie²⁴ and of Robinson and Draper²⁵ on the results of vagus pressure in man.

SUMMARY

In a case of sino-auricular heart block occurring in a man, 31 years of age, who is in apparently good health and clinically normal with the exception of the block and a moderate degree of cardiac hypertrophy, diagnosis of the condition was made by the aid of the electrocardiogram and venous pulse tracings. It has persisted under observations for ten weeks and from the history has probably been present for years. The type of block varies from a 2:1 partial sino-auricular block to only occasional blocking of systoles. At times an auriculoventricular or nodal rhythm was observed, present alone or combined with sinus block. Occasionally a normal cardiac rhythm was present. The block was found to be abolished by atropin, by deep rapid breathing, by swallowing movements, by exercise, and to be brought on or increased by pressure on the right vagus nerve in the cervical region. It is suggested that the condition results from an abnormal vagus tone. It was unassociated with auriculoventricular block. The rate of beat varies at different times from approximately 30 to 60 beats per minute, and shows a slow regular rhythm and a fast regular rhythm. The intermediate rates are always arrhythmic, due to the dropping of systoles in an otherwise regular rhythm. The slow regular rate is interpreted as a 2:1 sino-auricular block. The fast regular beat is due to a normal rhythm without block. In addition there was at times a somewhat slower regular rate of auriculoventricular or "nodal" origin.

23 The cardiac shadow area as measured by the method of Dietlen is 143.5 sq cm. The normal for a man of the patient's weight, according to Dietlen is about 120 sq cm. A sufficient explanation for the presence of the hypertrophy would seem to be present in the very slow heart rate that has apparently been present for many years. With a heart beating at from one-half to two-thirds the usual rate and yet maintaining a normal blood pressure, each beat must be correspondingly larger, a condition which in time would certainly lead to hypertrophy.

24 Ritchie. *Quart Jour Med*, 1912-1913, vi, 47.

25 Robinson and Draper. *Jour Exper Med*, 1911, xiv, 217.

CLINICAL STUDIES ON THE RESPIRATION NO 1

THE EFFECT OF CARBON DIOXID IN THE INSPIRED AIR ON PATIENTS WITH CARDIAC DISEASE *

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Recent physiologic investigations have shown conclusively that the most important factor controlling the respiration is the reaction of the blood. Through the agency of the kidneys, which excrete non-volatile acids, and the lungs, which excrete volatile acids, the hydrogen ion concentration of the blood is kept within the narrow limits which are compatible with life. A rise of the acidity of the blood above its normal level stimulates the respiratory center and increases pulmonary ventilation to such an extent that the tension of carbon dioxide is reduced and the normal reaction of the blood is upheld. Anything which causes an increase in the carbon dioxide tension of the blood results in an augmented ventilation of the lungs. Hence the dyspnea after moderate exercise, and the dyspnea produced by breathing an atmosphere containing high percentages of carbon dioxide. In the studies to be described in the present paper the fact that carbon dioxide acts as a stimulus to the respiration forms the basis of its use as a functional test. Subjects have been allowed to breathe air in which the amount of carbon dioxide was constantly rising, and their ventilation has been measured. Thus the effect which known percentages of carbon dioxide produced on the respiration could be readily determined, and curves could be plotted showing the increase in ventilation resulting from the rise of carbon dioxide in the inspired air.

The effect of carbon dioxide was first studied in a number of normal individuals of different ages and weights, and it was found that within rather narrow limits a given increase in the percentage of carbon dioxide in the inspired air produced a definite increase in the pulmonary ventilation. Thus a curve of the normal response to the stimulus could be established. Similar investigations were then made on pathologic patients in whom dyspnea had been a prominent factor. The cases here reported fall into two groups, those of pure cardiac disease, and those which are best described by the term "cardiorenal" disease. Since pathologic conditions underlying the dyspnea in these two classes of cases are apparently somewhat different, it is proper that the groups should be considered separately.

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* From the Medical Clinic of the Peter Bent Brigham Hospital

The use of carbon dioxid in the inspired air as a means of producing dyspnea in a functional test of the respiration has certain advantages. It is a comparatively simple method and affords ready and accurate determination of the amount both of stimulus and response. Furthermore, it gives a relatively uncomplicated picture of the results produced by a single factor. If, for instance, exercise is used as a means of producing dyspnea, the results are confused because the development of skeletal muscles, training, degree of adiposity, and the functional capacity of the heart all play important parts in determining the degree of dyspnea produced by a given amount of exercise. In using carbon dioxid in the inspired air as a test of respiration the stimulus can be graded, and a comparatively large effect on the ventilation may be obtained with a minimum of discomfort to the patient. As the test can be made with the patient lying quietly in bed, it may be safely applied to patients whom it would not be proper to move.

Two general methods were applicable. On the one hand one might give the subject air to breathe containing a fixed and known amount of carbon dioxid. Such a method was used by Lindhard¹ in his studies on the excitability of the respiratory center. Or it would be possible to use the "closed-circuit" method, in which the patient would rebreathe his own inspired air and would thus himself produce the carbon dioxid which should serve as the stimulus to respiration. This method was used by Hough,² but in his experiments no systematic analyses of the inspired air are recorded, so that they have a very indirect bearing on the present work.

THE METHOD

The subjects, sitting on a chair, or propped up in bed, breathe through valves which separate the inspired from the expired air, into a closed system. The valves are of glass with rubber flaps, of a form designed by Krogh. Respiration is through the mouth, the nose being tightly closed by a clip. The expired air passes into a large tin box holding about 27 liters. The expired air enters the box at the top and leaves by an outlet tube near the bottom, thus having ample opportunity for the diffusion of gases. Leaving by the outlet tube the air passes to a second tin box, similar in size and construction to the first and again allowing thorough mixing. From the lower part of this second box an outlet tube runs to the inspiratory valves. A small tube is inserted in the side of this second box through which samples of air may be taken for the determination of the composition of the inspired air. A short side tube, leading off from the tube connecting the two

1 Lindhard *Jour of Physiol*, 1911, xlii, 337

2 Hough *Am Jour Physiol*, 1911, xxviii, 369

tin boxes, runs to a small Krogh volumetric spirometer. The movements of the spirometer are recorded on the smoked paper of a kymograph, and by means of a calibrated scale the volume of each respiration can be accurately measured. A timer marking five-second intervals was used. The whole apparatus, with the exception of the valves and tubing leading to and from the tin boxes, was concealed by a screen, so that the subject's attention should not be distracted by the moving spirometer and kymograph.

In most instances a pneumographic record of the respiration was taken while the subject was at rest, and before breathing through the valves was begun. This gave the normal rate and some information as to the character of the respiration, but was of little value in giving evidence as to the depth of respiration. In other cases the respiration at rest was counted. The pulse rate at rest was also counted. The rubber mouthpiece was then put into the subject's mouth, connected with the valves, the nose clip put in place and the experiment started. A continuous record of the respiration was kept on the kymograph. Every two minutes a sample of inspired air was taken, and at the same time the pulse was counted. The experiment was continued until a degree of dyspnea was produced which caused discomfort or distress to the subject. As will be seen below, the length of the experiment depended on a number of factors and was variable. At the end of the experiment the samples of inspired air were analyzed. In all the earlier experiments both oxygen and carbon dioxide were determined, but as the oxygen fell to a degree that was quite parallel to the rise of carbon dioxide, and as the oxygen rarely got so low as to be a significant factor in the production of the dyspnea, the analysis of samples from the later experiments was usually limited to the determination of carbon dioxide. In all cases, however, in which the carbon dioxide in the inspired air had risen especially high, the oxygen was also determined. With an adult of average size the carbon dioxide concentration reached 6 per cent in about fifteen minutes, and at this time the oxygen would have dropped to approximately 13 per cent. In one unusual experiment the subject continued breathing until the carbon dioxide had risen to 9.06 per cent, and the oxygen had fallen to 8.96 per cent. From the kymographic record of the respiration the rate, volume per respiration, and the total ventilation per minute were calculated. When the respiration was regular the total ventilation was determined by multiplying the rate by the volume of a single respiration, but when it was irregular the volume of each respiration during a minute was measured. The percentage of carbon dioxide in the inspired air was then compared with the total ventilation during one minute. The minute over which the total ventilation was measured was so

chosen as to end just after the sample of air was taken. The relation between the total ventilation and the carbon dioxide in the inspired air is best shown graphically by means of a chart on which the abscissae represent the percentage of carbon dioxide in the inspired air, and the ordinates show the percentage increase in the total ventilation. The total ventilation during the second minute was in most cases (see below) assumed to be the resting value, and charted on the base line (100). The ventilation of subsequent minutes is charted in terms of percentage increase of this figure. The figure representing the percentage increase has been termed the ventilation coefficient. Thus when the ventilation doubled its initial value, the coefficient is 200. A coefficient of 300 signifies a ventilation which is three times the resting amount. A curve may thus be plotted which will show the increase of ventilation corresponding to the increase of carbon dioxide in the inspired air.

There are various limitations and sources of error in an experimental procedure such as that outlined. It would undoubtedly be better to study the effect of increasing carbon dioxide on alveolar ventilation rather than on total ventilation, since the alveolar ventilation is the important factor to the organism. Lindhard¹ has made this point clear in his work on the excitability of the respiratory center. The determination of alveolar ventilation, however, requires a knowledge of the size of the dead space, and at present when both the methods of determining the dead space and the possibility of there being considerable variation in the size of the dead space under physiologic and pathologic conditions are being actively debated, it seemed wiser to study only the total ventilation. Determinations of the dead space in some patients would have been a very difficult problem.

Another point which makes for inaccuracy in the curves is the fact that the air analysis represents the composition of the inspired air at only one particular instant of the minute over which the ventilation was being measured. This is not especially important, however, as the system was so large that the percentage of carbon dioxide rose rather slowly. Of more significance are the errors which depend on making an untrained subject breathe through the mouth. Frequently the character of the respiration is changed from the normal, usually in the direction of somewhat slower and deeper breathing. Subsequent questioning often brought out the fact that the subject was wholly unaware of this change, and after the first few breaths felt no discomfort from mouth breathing. It seems probable that although the character of the breathing was altered, the alveolar ventilation remained practically unchanged. There was usually only slight change in the total ventilation during the first five minutes of the experiment, as the carbon

dioxid in the inspired air was but little over 1 per cent The rise in the ventilation in this period was rarely more than 10 to 15 per cent over that during the second minute The value during the second minute was usually assumed to be the "initial ventilation," and at this

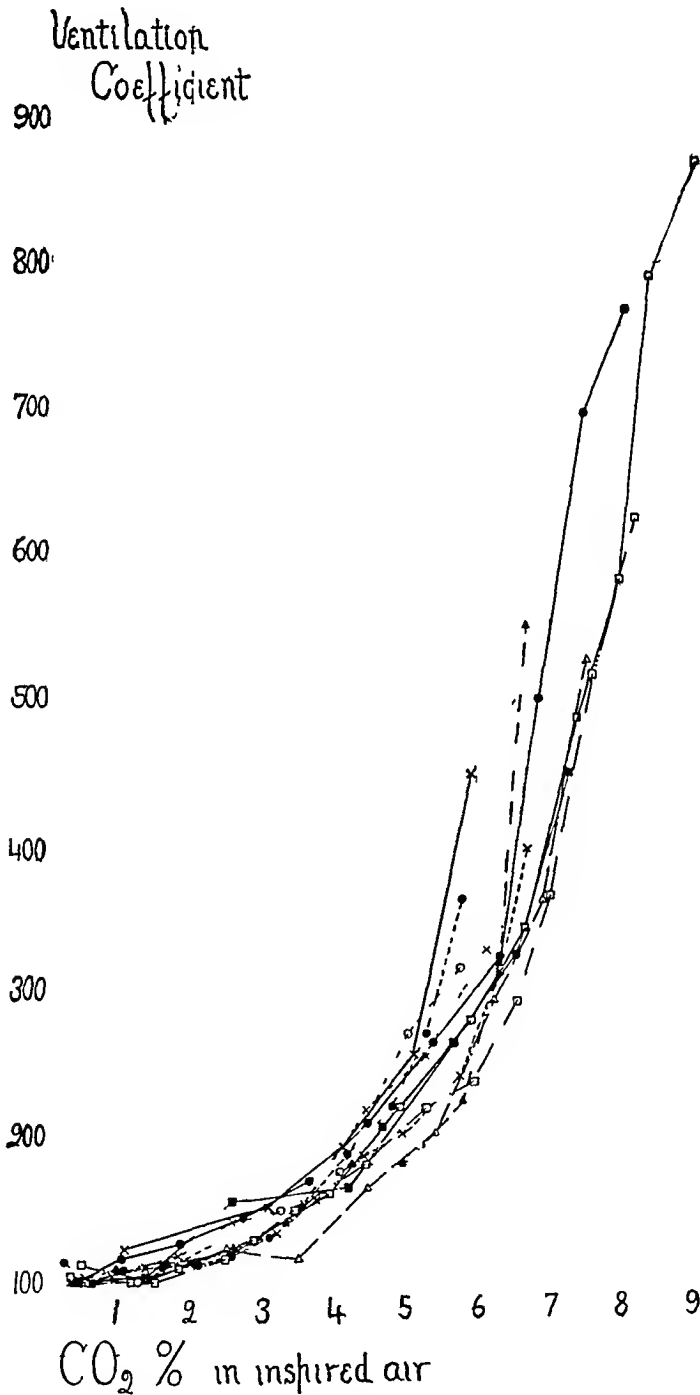


Fig 1—Ordinates percentage increase in minute volume of ventilation
 Abscissae percentage increase in carbon dioxid content of inspired air The curves show the response of a series of normal subjects to increasing amounts of carbon dioxid The ventilation is doubled when the inspired air contains 4.3 to 5.4 per cent carbon dioxid

time the carbon dioxid was not often over 0.3 per cent. In some instances the ventilation in the fourth minute was less than in the second, due apparently to the fact that the subject took longer to get accustomed to the apparatus. Under these circumstances the later and lower ventilation is charted as the resting value (100). Another factor which tends to diminish the absolute accuracy of the records is the slight irregularity of the response of an individual subject to the same stimulus on different occasions. In two or more experiments on the

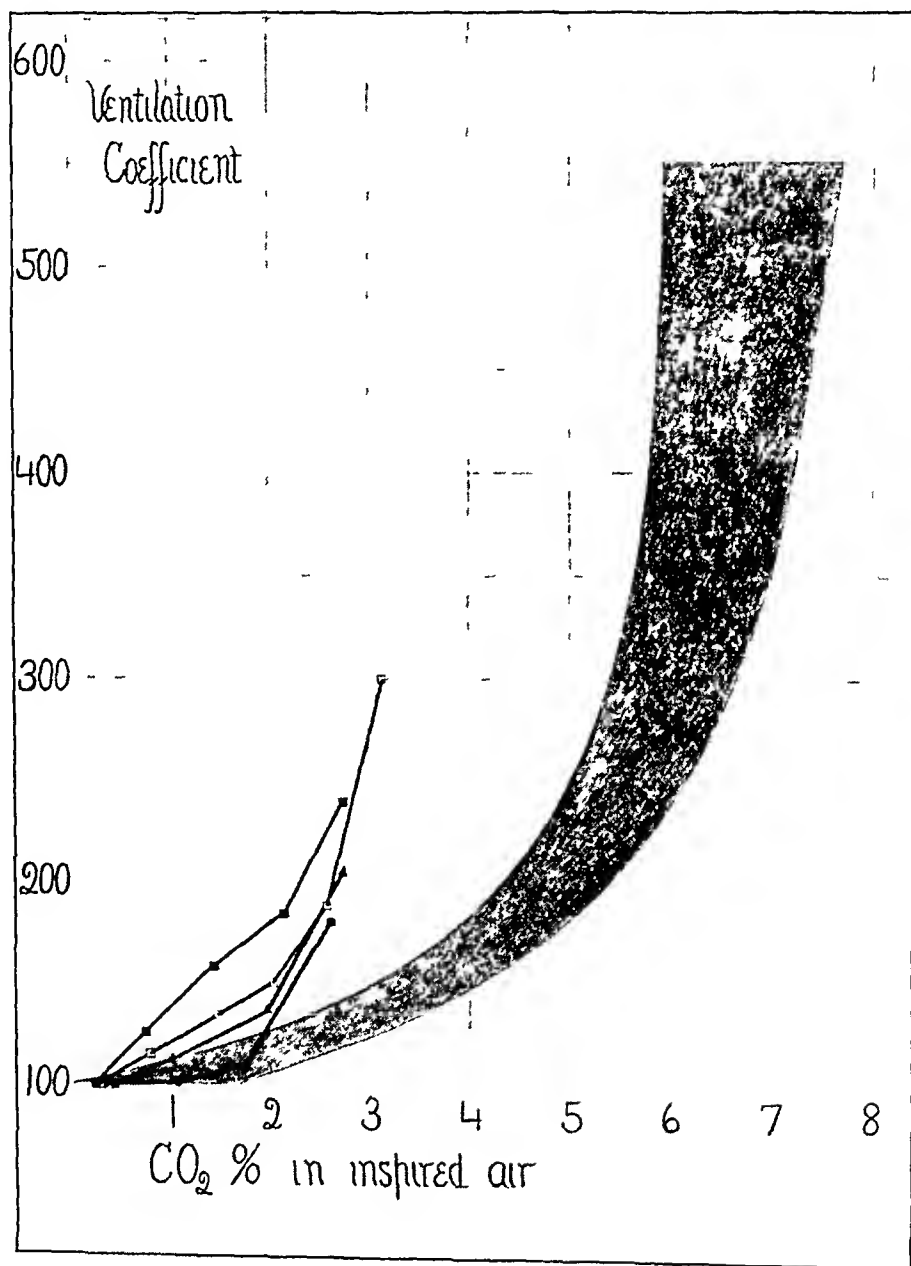


Fig 2—Ordinates percentage increase in minute volume of ventilation. Abscissae percentage increase in carbon dioxide content of inspired air. The shaded curve shows the response of normal subjects to increasing amounts of carbon dioxide. The ventilation is doubled when the inspired air contains 4.3 to 5.4 per cent carbon dioxide. The black lines show the response of patients with acidosis. The ventilation is doubled when the inspired air contains only 2 to 3 per cent carbon dioxide.

same subject the points on the curve are rarely exactly superimposed, owing probably to varying psychic and metabolic conditions. However, perhaps the most striking feature which has come out of the observations on normal individuals is the fact that in spite of these chances for error and inaccuracy there is a very definite curve of response which will serve as a normal, and may be used for comparison with pathologic conditions.

NORMAL SUBJECTS

The normal subjects on whom observations were made represent various sizes and types. Several were young men who had been athletes, and were in good training at the time of the experiments. Among the others were medical students and physicians accustomed to little exercise and rather easily winded. One subject was a young man in first-class training weighing 205 pounds, while another was a slim girl of 14 whose weight was 98 pounds. The rest fell in between these extremes. The experiments revealed no differences in the reaction to carbon dioxide which bore any relation to age, size, or weight.

Chart 1 shows the curves representing the response of nine normal individuals to increasing amounts of carbon dioxide in the inspired air. It will be noted that in spite of the variations of single points, and of the differences in individuals, all the curves follow the same general line. There is at first a very slow increase in ventilation. By the time the carbon dioxide has reached between 3 and 4 per cent, the ventilation is in most cases one half again as great as normal. Then follows a sharper rise of the curve so that when the carbon dioxide is between 4.2 and 5.4 per cent the total ventilation has doubled. Beyond this point greater individual variations begin to show themselves, and small increases in the carbon dioxide cause much greater increase in the total ventilation. Above the line marked 300, the point at which the ventilation has been trebled, the chart is of less significance from the point of view of the present study, but certain facts of interest may be brought out. In performing the experiments it was intended that the subjects should continue until dyspnea became uncomfortable or until they became slightly dizzy. The majority continued breathing until the inspired air contained from 5.5 to 7 per cent carbon dioxide. • Those who were able to go on until they were breathing air containing from 7.5 to 9 per cent carbon dioxide were all individuals who were capable of producing an extremely large ventilation, and as it happened, were the men who had been most athletic and were in the best training. K. L. D., who breathed the highest percentage of carbon dioxide and whose ventilation became more than eight times the normal, was the largest subject, and probably the most highly trained. F. G. B., who went easily to 8.2 per cent carbon dioxide, and whose

ventilation was above six times the normal, is medium sized. On the other hand, E H, the girl mentioned above, was able to breathe a mixture containing 67 per cent carbon dioxid without discomfort, her ventilation rising to nearly four times the normal. Both carbon dioxid and ventilation were in her case higher than in the experiments done with some of the men who were much larger and stronger. Thus no direct relationship exists between the age, size, or weight of a subject and the percentage of carbon dioxid which they can breathe. The percentage of carbon dioxid which can be breathed without discomfort seems to depend on the ability to increase the ventilation.

As in the experiments of Hough,² it was found that some persons increase their ventilation chiefly by increasing the rate, while others depend chiefly on increase in depth. The majority begin by increasing the volume of each inspiration, then later increase the rate, so that toward the end of the experiment both rate and depth are much above normal. The time of the experiment was very variable and depended on the rate at which carbon dioxid was produced by the subject. The average subject was breathing approximately 5 per cent carbon dioxid at the end of about twelve minutes. K L D, a large individual, was breathing 9.06 per cent carbon dioxid at the end of twenty-three minutes, while W L B, a small man, was breathing only 5.78 per cent carbon dioxid after twenty-four minutes. Thus on account of variations in rate of production of carbon dioxid in persons of different size and of different metabolic activities, the time element is of no significance. Hough has already called attention to the fact that in order to get comparative curves the size of the closed system must be adapted to the size of the subject. In the present work this difficulty is avoided as the time element is neglected, and the carbon dioxid content in the inspired air is the factor compared with the ventilation.

Table 1 shows the chief data at the beginning and at the end of the experiments on normal individuals.

Pulse Rate—The pulse rate was taken every two minutes during the experiment, at the same time at which samples of inspired air were taken for analysis. In general the pulse rate increases very slightly with the increase of respiration. By the time the ventilation was doubled the pulse rate had usually risen only 2 to 10 beats per minute. In several instances it was slower than at the beginning of the experiment. The pulse rate remained practically unchanged at the time at which the ventilation was trebled. With the ventilation quadrupled the pulse rate was rarely more than 10 beats per minute above its rate at rest. Only occasionally during the last two minutes, when the subject was pumping hard, would the pulse rate become as much as

TABLE 1—NORMAL SUBJECTS

Subject	Rate of Respiration		Single Respiration, c c		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent CO ₂ in Inspired Air at End
	Initial	Final	Initial	Final	Initial	Final		
F G B	14	22	818	3,291	13 09	72 41	622	8 20
W M B	22	22	352	1,268	8 82	27 90	360	5 78
D W C	24	36	450	900	10 80	32 40	313	5 75
E C C	12	22	822	2,346	9 86	51 61	524	7 52
E C	14	25	608	1,902	8 69	47 56	548	6 67
K L D	10	20	695	2,668	6 95	53 37	767	8 06
	10	17	800	2,100	8 00	35 75	446	7 27
E H	21	28	350	1,038	7 35	29 05	395	6 70
F W P	11 5	18	600	1,600	6 90	30 80	446	5 92
N S S	14	19 5	600	1,400	8 40	27 30	325	6 12

20 beats per minute above normal. This brings out an interesting difference between dyspnea produced by breathing high percentage of carbon dioxide and the dyspnea caused by exercise. In the latter one would expect a much greater rise in pulse rate with a corresponding degree of dyspnea.

PATHOLOGIC CASES

The pathologic cases studied with the method just described are all instances of cardiac or of cardiorenal disease. It was hoped that some light would be thrown on the mechanism of the production of dyspnea in these conditions. There is a considerable body of evidence to show that different factors take part in causing dyspnea in these two groups of cases. In the pure cardiac cases the dyspnea seems to depend on a slow or insufficient circulation, which results in a poor oxygenation of the tissues, and may even cause a transient acidosis owing to the incomplete combustion of metabolic products. In the cardiorenal cases this may be complicated by the presence of a considerable permanent acidosis, depending on imperfect renal excretion. In the present paper these groups are therefore taken up separately. Moreover, in order to obtain as clear an understanding of the subject as possible, a further subdivision has been made, depending on whether or not the cardiac condition was "compensated" at the time of the experiment.

I CARDIORENAL DISEASES

A Decompensated Cases—Four cases fall into this group, and on one of them observations were made on two occasions ten days apart. All of these patients showed slight, moderate or rather severe dyspnea.

A common characteristic of their respiration was its periodicity or tendency to be of the Cheyne-Stokes type. Periods of true apnea of over a few seconds duration were not seen at the time when the observations were made, and sometimes the periodicity was not noticed until pneumographic tracings were made. It usually became less evident after the patient began to breathe through the valves, and disappeared when the percentage of carbon dioxide in the inspired air began to rise. The disappearance of Cheyne-Stokes respiration under the influence of an increased concentration of carbon dioxide in the air breathed has frequently been observed before. The phthalein test showed an output for two hours of 15 per cent for J P C, of 65 per cent for J W O'M, and of 40.5 per cent for D N. The latter patient showed marked arteriosclerosis. All of these patients were in the terminal stage of their disease, although two of them were still living some weeks after the dates on which they were studied. From the point of view considered here, the most important and characteristic feature which these cases shared in common was the existence of an acidosis. This was shown by the low tension of the carbon dioxide in the alveolar air.

The initial ventilation varied from 9.5 to 15.99 liters, and was higher than would be expected in normal persons of the same size. Under the influence of carbon dioxide both the rate and the depth of respiration became increased, but the concentration of carbon dioxide which the patient could breathe was much below that tolerated by normal subjects. One patient was able to continue breathing until his ventilation was a little more than three times what it was at rest. It was necessary to stop the others when their ventilation was somewhat more than doubled or even before this. The total ventilation, when the observation was discontinued on account of dyspnea, was from 18.81 to 28.6 liters. With the normal subject the ventilation at the end was from 3.25 to 8.7 times as great as at the beginning and amounted to from 27.3 to 72.41 liters. Still more striking was the rate of the response. While the normal subjects doubled their ventilation when the carbon dioxide in the inspired air was approximately from 4.2 to 5.4 per cent, these patients increased their ventilation much quicker, and with a much lower percentage of carbon dioxide. In other words, they reacted to a lower stimulus. Table 2 shows the total ventilation, percentage of carbon dioxide in the inspired air and ventilation coefficient at the end of the observation, as well as the alveolar carbon dioxide tension in each case. The alveolar air was taken by the Plesch-Higgins method.³

³ Boothby and Peabody. *THE ARCHIVES INT. MED.*, 1914, xiii, 497.

TABLE 2—CARDIORENAL DISEASE, DECOMPENSATED CASES

Subject	Rate of Respiration		Single Respiration, c c		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent CO ₂ in Inspired Air at End	Alveolar CO ₂ Tension, mm
	Initial	Final	Initial	Final	Initial	Final			
J P C	21.5	25			10.37	18.81	181	2.62	34.5
C J D	18	31	672	803	12.10	24.90	203	2.74	34.6
D N	14	26	690	1,100	9.52	28.60	300	3.14	29.2
	19	27	500	850	9.50	22.85	240	2.74	26.9
J W O'M	20	32	516	841	15.99	26.52	172	3.69	36.1

J W O'M would practically fall into the normal group as far as the rate of his response is concerned. He was, however, markedly dyspneic when he was breathing air containing 3.69 per cent carbon dioxide, and could not readily increase his ventilation coefficient above 172. It is noteworthy that this is the highest alveolar carbon dioxide in the group.

Chart 2 shows graphically the response of these subjects. The shaded area indicates the normal field of response to the increasing carbon dioxide, and the lines illustrate the effect produced on some of the patients with acidosis.

Pulse—Satisfactory pulse records were obtained in only three observations. With D N the pulse rose from 78 at rest to 108 when the ventilation coefficient became 334, and from 98 to about 117 when the ventilation coefficient was 240. The patient had auricular fibrillation. On this, and in all patients with auricular fibrillation, the heart rate was determined by auscultation at the apex, and not by palpation of the arterial pulse. The pulse rate of J W O'M rose from 88 to 104 when the ventilation coefficient rose to 172. On the whole the pulse rate seemed to be slightly more affected than in the normal individuals, but when it is considered that both sets of patients were extremely dyspneic, the difference in pulse rate is very slight. The pulse rate varies with the degree of dyspnea. It is certain that muscular exercise sufficient to produce the amount of dyspnea which these patients exhibited would have caused a much greater rise in pulse rate.

B Compensated Cases—Four subjects, two of whom were also studied during a period of decompensation and have been considered in the last section, belong in this group. These were all cases of definite cardiorenal disease in whom the nephritis seemed to be the prominent factor. Dyspnea was not noticeable while the patients were at rest, but was easily produced by exertion. Pneumographic tracings brought out the fact that irregular respiration, with a tendency

to periodicity, was a common characteristic. It is important that the alveolar air examinations in all of these cases showed a normal carbon dioxide tension, thus demonstrating that no high grade of acidosis was present.

The subject P C, the mildest case, had chronic nephritis with hypertension and high-grade emphysema. His phthalein output was normal. E L W had a chronic nephritis with hypertension and a phthalein output of 36 per cent. He complained of considerable dyspnea on slight exertion. J W O'M had chronic nephritis with hypertension and his phthalein excretion was 10 per cent in two hours. He had marked dyspnea on exertion, and gave a history of severe sudden attacks of nocturnal dyspnea. He had such an attack the night before this observation was made. The patient gradually became worse and was studied again (as reported in the last section) a month later when he had begun to have dyspnea while at rest, and when his alveolar carbon dioxide tension had dropped below normal. Case J P C was also reported on in the last section. He had a chronic nephritis with a phthalein output of 15 per cent. Strictly speaking, this case should probably be grouped among the decompensated cases, as there was no essential difference in his clinical condition at the times of the two observations. On both occasions he had orthopnea with irregular and periodic breathing. In order to test accurately the relation of the acidosis to the increased sensitiveness shown by the last group of cases to carbon dioxide, it was decided to attempt to overcome the acidosis in this patient by administering alkali. It was necessary to give 95 gm sodium bicarbonate before the urine became alkaline. The alveolar air was then taken, and the carbon dioxide tension found to be 47.3 mm, somewhat above the usual normal limit. It is on account of the absence of acidosis that this observation was considered in the present group. It is a fact of considerable importance that although there was very little change in his general condition, the effect produced on his ventilation by carbon dioxide in the inspired air was now exactly similar to that produced in normal persons.

The observations on this group of cases show that their reaction to the increasing carbon dioxide in the inspired air is no more rapid than it is in the normals, in spite of the fact that they have a much greater tendency to dyspnea on exertion. The total ventilation did not become doubled until the carbon dioxide in the inspired air had reached approximately 45 per cent. The concentration of carbon dioxide which they could breathe without too intense dyspnea is below that which the normal controls could breathe. Both the total ventilation and the ventilation coefficient are distinctly below the normal average. J C

could have continued breathing longer, but as he was rather sick the observation was stopped as soon as dyspnea began. He said that he "felt a little short-winded but could have stood it a few minutes more." Table 3 shows the alveolar carbon dioxide tension as well as the essential data at the beginning and the end of the observations.

TABLE 3—CARDIORENAL DISEASE, COMPENSATED CASES

Subject	Rate of Respiration		Single Respiration, c c		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent CO ₂ in Inspired Air at End	Alveolar CO ₂ Tension, mm
	Initial	Final	Initial	Final	Initial	Final			
P O	9	22	772	1,285	6.95	28.26	407	6.58	46.1
J P O	17	23			7.84	15.08	193	4.66	47.3
J W O'M	15	26			10.18	25.86	254	4.97	42.8
E L W	14.5	14	550	1,200	7.98	16.80	210	4.42	45.1

Pulse—The rise of pulse rate during the observation agrees well with what was seen in the normal subjects and was approximately from 10 to 20 per minute.

II CARDIAC DISEASE

A Decompensated Cases—Four cases of valvular disease may be grouped under this heading. All of the patients showed orthopnea and a moderate amount of dyspnea even while they were at rest in bed. Three of these patients were studied twice on two successive days and will be considered together, as they had a low alveolar carbon dioxide tension, a feature which seems to be of considerable importance. The carbon dioxide tension varied from 30.9 to 37.7 millimeters. This moderate depression has been found to be present in many instances of pure cardiac dyspnea during the most acute stage. It passes away quickly as soon as the patient begins to get compensated. Cyanosis was not especially striking in any of the cases, but its presence was noted in two of the patients. Periodic respiration was observed in two cases. On the whole the effects produced by inspiration of air containing increased amounts of carbon dioxide were about the same as with the decompensated cardiorenal cases. It required less carbon dioxide to induce dyspnea than was needed with the normal subject. While the total ventilation is normally doubled by breathing air containing 4.2 to 5.4 per cent carbon dioxide, in these patients it was doubled by air containing between 3 and 4 per cent carbon dioxide. There is apparently a fairly close relationship between the alveolar air and the pulmonary response, in that the lower the alveolar carbon dioxide tension, the less the concentration of carbon

dioxid in the inspired air that is required to produce a given increase in the ventilation. The concentration of carbon dioxid which the patients could breathe was much lower than that which normal individuals are able to stand. The total ventilation at the end of the observation, when the dyspnea was at its height, was much less than the average normal, and the ventilation coefficients were far below the values with normal subjects. The figures for R B do not represent her maximum effort, as the experiment was stopped shortly after the onset of dyspnea in order not to fatigue her too much.

One case formed an exception to the above statements. M M, with chronic valvular disease, was studied at a time when he had considerable dyspnea, although he was lying quietly in bed propped up on a back rest. He had only slight cyanosis. The alveolar carbon dioxid tension was 42.4 millimeters. He thus corresponds to the group of decompensated cardiac cases without acidosis, as described by Lewis. The experiment with this patient showed that he could breathe a much higher concentration of carbon dioxid (5.16 per cent) than could those decompensated cases which had an acidosis. In spite of the fact that he was very dyspneic at the end of the observation, his total ventilation rose only from 12.65 to 20.8 liters, and the volume of the single respiration from an average of about 575 cubic centimeters to about 650 cubic centimeters. This patient differed again from the other decompensated cases in that his ventilation coefficient rose only to 1.65 when there was 5.16 per cent carbon dioxid in the inspired air. Thus he did not show the sensitiveness to carbon dioxid which was characteristic of the other patients with dyspnea. Indeed, his ventilation increased less rapidly under the influence of the added stimulus than did that of the normal individuals.

TABLE 4—CARDIAC DISEASES, DECOMPENSATED CASES

Subject	Rate of Respiration		Single Respiration, c c		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent CO_2 in Inspired Air at End	Alveolar CO_2 Tension, mm
	Initial	Final	Initial	Final	Initial	Final			
R B	24	31	200	450	7.71	14.44	1.87	3.43	35.2
J H B	17	24			9.55	26.63	2.79	4.10	37.7
	18.5	24			11.58	25.36	2.19	3.70	34.3
W M	19.5	27	410	600	8.00	16.20	2.02	3.41	30.9
M M	22	32	575	650	12.65	20.80	1.65	5.16	42.4

Table 4 shows the alveolar carbon dioxid tensions and the various factors of importance at the beginning and the end of observations on the cardiac cases with decompensation.

Pulse—The rise in pulse rate during the observation was not over 15 per minute in three cases. In W M the rate rose from 108 to 154 when his total ventilation doubled. This was a patient with auricular fibrillation. During one observation the pulse rate of J B rose from 86 to 100 per minute. After he was completely rested the effect of exercise was tried, by making him sit up and lie down in bed seven times. This pulse rate rose from 82 to 100 per minute, but his dyspnea was much less than it was in the carbon dioxide experiment.

B Compensated Cases—Ten patients with cardiac disease, valvular or myocardial, were examined at a stage when their hearts were so well compensated that they had no dyspnea while they were at rest in bed. In all of them dyspnea was easily produced by slight exertion. A total number of 17 experiments was performed on this group. Four of the patients had been previously studied during the period when they were decompensated and were having dyspnea even while at rest. In all the subjects of this group the alveolar carbon dioxide tension was normal, and there was no evidence of acidosis. The percentage of carbon dioxide in the inspired air which these patients were able to breathe was higher than that which the decompensated cardiac cases were able to take, but was not on the whole as high as the normals could breathe. As the dyspnea increased the size of the individual respirations increased, more so than with the decompensated patients, but in general less than with the normals. The total ventilation was also greater than in the decompensated group, but less than in the normal subjects. Although in considering this point it must be borne in mind that the sick patients were stopped before they became quite so breathless as the normal individuals were allowed to become, it appeared to be quite definite that the extent to which they were able to increase their pulmonary ventilation was distinctly limited. This is also brought out by comparing the ventilation coefficients of the two groups. The percentage increase of ventilation as shown by the ventilation coefficient rose, in its relation to the carbon dioxide of the inspired air, exactly as in the normal subjects. The ventilation became doubled when air containing between 4.2 and 5.4 per cent carbon dioxide was being breathed. There was thus no hypersensitivity to carbon dioxide as was manifested by the decompensated cases with acidosis. This is especially interesting when it is remembered that exercise would produce dyspnea in these patients very much more easily than in healthy persons, and again shows that the test employed here has quite a different influence on the respiration than has physical exercise.

Two cases proved to be exceptions to the above statements. W E M was studied on two occasions over a week apart after his dyspnea had disappeared, and after his alveolar air had become nor-

mal He could stand a higher percentage of carbon dioxide, and both his total ventilation and ventilation coefficient increased much more than before he became compensated, but he remained hypersensitive to carbon dioxide, and doubled his ventilation under the influence of 2 to 3 per cent carbon dioxide It is noteworthy that he was the sickest patient in this group W M, the patient who while still dyspneic had a normal alveolar carbon dioxide tension, showed a hyposensitiveness to carbon dioxide in that when he was breathing 5.32 per cent carbon dioxide, his ventilation coefficient was only 163 This was exactly similar to what was observed on the previous occasion before he regained his compensation However, at the second experiment the degree of dyspnea produced was not so great as at the first, although the percentage of carbon dioxide was just the same Table 5 shows the essential features of this group

TABLE 5—CARDIAC DISEASE, COMPENSATED CASES

Subject	Rate of Respiration		Single Respiration, c c		Total Ventilation per Minute, Liters		Ventilation Coefficient at End	Per Cent CO ₂ in Inspired Air at End	Alveolar CO ₂ Tension, mm
	Initial	Final	Initial	Final	Initial	Final			
S G B	19	28.5	675	850	12.74	24.30	191	3.92	39.3
	20.5	24	450	850	9.24	20.40	221	4.53	40.0
R B	20	30	535	775	10.71	23.02	216	4.85	39.2
J H B	15	24	610	1,650	9.39	39.59	421	6.99	49.8
J H S	20	27	400	600	8.00	16.20	203	4.59	
	21	26	475	1,000	9.97	26.00	261	6.19	
A F	17.5	20.5	500	925	8.53	19.88	233	5.90	47.3
G	18	19	400	822	7.20	15.62	217	5.40	36.2
T H	19	21.5	450	1,300	8.56	28.00	327	6.75	
	20	22.5	475	1,100	9.50	24.78	262		45.0
	19	22	525	1,150	9.98	25.30	253	5.97	
J S	22	24	450	700	9.90	16.80	170	4.48	
	23	36	450	800	10.35	28.00	270	5.62	43.5
	24.5	26	475	900	11.65	23.40	201	4.97	45.2
W M	14.5	39	450	600	6.52	23.40	360	4.60	38.1
	12	39	520	775	6.36	30.50	480	4.95	41.6
M M	18.5	23	700	950	12.95	21.80	163	5.32	

Pulse—The greatest rise in pulse rate during these observations was 16 per minute In most instances it was much less In two cases a little exercise, insufficient to produce noticeable dyspnea, caused considerably greater rises in the pulse rate

SUMMARY AND DISCUSSION

Experiments are described in which normal subjects and patients with cardiac or cardiorenal disease have breathed air containing

increasing amounts of carbon dioxide. The inspired air was analyzed for its carbon dioxide content, and the total ventilation of the subject per minute was measured at frequent intervals. Thus the increase in ventilation caused by a given rise of carbon dioxide in the inspired air could be easily determined. It was found that normal persons respond to carbon dioxide in a fairly constant manner, and that their total ventilation is doubled when the carbon dioxide is between 4.2 and 5.4 per cent. Cardiac and cardiorenal patients whose circulation is compensated, and who have no evidence of an acidosis as shown by the carbon dioxide tension of the alveolar air, behave in an exactly similar manner. Cases, however, with decompensation and with a grade of acidosis sufficient to lower the alveolar carbon dioxide tension react much more quickly to the carbon dioxide, and may double their ventilation when the carbon dioxide is only 2 to 3 per cent of the inspired air. Dyspnea is therefore much more easily produced in the patients with acidosis than in those without acidosis. That the increased sensitiveness to carbon dioxide does in fact depend on the acidosis was especially clearly demonstrated in two cases. In one of these (J. W. O'M.) an observation made after the development of acidosis showed him to be more easily affected by carbon dioxide than he had been at a previous examination before the acidosis appeared. The second (J. P. C.) was extremely susceptible to carbon dioxide at a time when he had an acidosis, but after this had been overcome by large doses of sodium bicarbonate, in spite of the fact that his clinical condition had not improved, his reaction to carbon dioxide became exactly similar to that of normal individuals. Although the results reported relate only to the dyspnea caused by the inspiration of air containing carbon dioxide, it is wholly logical to assume that the same effect would be produced by acids which entered the blood stream from the body cells. The presence of an acidosis would thus render the organism more sensitive to the carbon dioxide or other acids formed during muscular work, and the amount of muscular work sufficient to cause dyspnea would be less than under normal conditions.

The explanation of these observations appears to be comparatively simple. Under normal circumstances the "buffer" action of the bicarbonates, phosphates and proteins in the blood is so great that a large amount of acid can be taken up without any significant change in the hydrogen ion concentration being produced. When, however, an acidosis is present which is severe enough to cause a depression of the carbon dioxide tension of the blood this mechanism for the preservation of the normal reaction of blood has begun to break down. The blood has already taken up nearly as much acid as it can without its reaction changing. When even a small additional amount of acid is

introduced into the blood there is an alteration of the hydrogen ion concentration, and a consequent stimulation of the respiratory center. Recent experiments by Christiansen, Douglas and Haldane⁴ have a direct bearing on this subject. These authors found "that the presence of lactic acid in the blood" after severe exercise "led to an enormous temporary alteration in the absorption curve" for carbon dioxide, and they suggest that "corresponding differences in the normal absorption curve will probably be discovered under various pathologic or compensatory conditions of 'acidosis'." The experiments reported here do not appear to give any information regarding possible changes in the excitability of the respiratory center in the pathologic conditions studied.

The importance of the observations lies in the fact that they throw some light on the part played by the acidosis in the production of dyspnea in cardiac, and especially in cardiorenal disease. The degree of acidosis, as indicated by the alveolar carbon dioxide tension, is, even when dyspnea is marked, rarely great in these conditions. A similar amount of acidosis in diabetes may cause no gross changes in the respiration. Moreover, the deep, regular breathing of diabetic coma, which is accepted as being the typical effect of acidosis, is wholly unlike the shallow, rapid, irregular respiration seen in cardiorenal dyspnea. It seems to be improbable that the acidosis is the sole cause of the dyspnea, but the experiments indicate that it is a contributing element, since it tends to break down the mechanism by which the normal reaction of the blood is maintained. A subject with even moderate acidosis is rendered abnormally susceptible to any increase of the acid in his blood. Thus it is that certain patients with advanced chronic nephritis and low alveolar carbon dioxide tension have no dyspnea as long as the heart is sufficient, but as soon as the circulation begins to fail so that carbon dioxide and perhaps lactic acid accumulate in the blood the effect on the respiration is greater than it would be in a subject whose blood was normal. The extent to which the acidosis is involved in causing the dyspnea will depend on its severity and will vary from case to case.

The addition of carbon dioxide to the inspired air affects the respiration and produces little influence on the circulatory system. In normal persons the pulse rate only rises slightly even when the dyspnea is great. The same is true of compensated cardiac cases. A somewhat greater increase in pulse rate may be seen in the decompensated cases, but it is much less than the pulse rate which would be brought about if a similar degree of dyspnea were caused by exercise.

4 Christiansen, Douglas and Haldane Jour Physiol, 1914, xlviii, 244

CONCLUSIONS

1 Normal individuals are affected in a fairly constant manner by breathing air containing increasing amounts of carbon dioxide. In the experiments reported the total ventilation was doubled when the concentration of carbon dioxide was between 4.2 and 5.4 per cent.

2 Patients with cardiac and cardiorenal disease, who are without acidosis, as indicated by the alveolar carbon dioxide tension, react in a manner similar to normal subjects.

3 Patients with cardiac and cardiorenal disease, with acidosis, are much more susceptible to the carbon dioxide in the inspired air. Dyspnea is more easily produced than in normal subjects or in patients without acidosis, and the ventilation may be doubled when the inspired air contains only 2 to 3 per cent carbon dioxide.

4 While acidosis is probably not the sole factor causing the dyspnea in cardiac and cardiorenal disease, it may be an element of considerable importance in producing the clinical picture.

POISONING BY MERCURIC CHLORID AND ITS TREATMENT*

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The recent increase in the number of cases of poisoning by mercuric chlorid is largely due to the newspaper notoriety which was given to a case of accidental poisoning occurring about four years ago. The public were instructed in all the details of the symptoms, and great stress was laid, not only on the sureness of the fatal ending, but also on the painlessness and lack of suffering which accompanied the week-long illness of that particular victim. The repetition of similar publications and the ease with which tablets of the drug could be obtained appealed to would-be suicides, and now both intentional and accidental cases of poisoning have become a common occurrence in hospital practice. Mercuric chlorid tablets have been used for some years as a household article to treat the ordinary slight wound infections of the family, to rid the house of bed vermin, and in many cases as a preventive of conception.

The commonest accident resulting in poisoning is the swallowing of the tablets in mistake for some headache remedy. Such accidental cases about equal in number those of attempted suicide. In New York City the cases of suicide by poisoning, due to the principal drugs, for the past twenty-five years, are shown in Table 1, arranged in five-year periods.

This table shows that there is a fashion in the methods of suicides, and that poisoning by arsenic and Paris green and by phenol (carbolic acid) are on the decrease, that by opium is stationary, while poisoning by illuminating gas and mercuric chlorid are both becoming popular methods and are on the increase. Of the 155 cases of suicide by mercuric chlorid recorded in the past twenty-five years, seventy-three, or nearly half of them, have occurred in the last two years. This question, therefore, forms an important social problem. The regulation of the sale of the poison in the form of antiseptic tablets of corrosive sublimate is already begun, and should be undertaken and enforced by all boards of health.

The symptoms of poisoning by mercuric chlorid came into prominence and were studied first as a complication of surgical operations and in obstetric practice. The drug was introduced as an antiseptic

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in the early eighties, and has been widely used ever since. In the cases of wound absorption, the initial toxic gastritis is absent, and the kidney symptoms and salivation are less prominent than the colitis. The absorption of the drug is gradual in these cases, and its effect is shown in great part in the efforts of the large intestine to eliminate it, with the result of an intensive and often fatal ulcerative colitis. A case of mercuric chlorid poisoning, resulting from the surgical accident of delivering about $1\frac{1}{2}$ grains of the salt into the vein of a patient during a postoperative saline infusion, gave the following sequence of events, and throws much light on the symptomatology of the condition. The symptoms in this case are not the same as those which result from absorption from surgical wounds, but resemble the cases of poisoning with a predominance of kidney and intestinal symptoms.

TABLE 1—SUICIDES IN NEW YORK BY POISONING, 1890-1914

Poisons	1890-1894	1895-1899	1900-1904	1905-1909	1910-1914
Paris green and arsenic	155	170	99	47	48
Phenol	73	627	1,455	325	154
Opium and morphin	42	56	56	48	29
Mercuric chlorid	4	10	9	28	104
Illuminating gas	65	315	628	1,149	1,554
Other poisons	58	94	104	196	237
Total all poisons	397	1,272	2,351	1,793	2,126

Figures from 1890 to 1897 inclusive represent former City of New York

Figures from 1898 to 1914 inclusive represent Greater New York

The infusion was given on the fifth day after a laparotomy. Prior to the giving of the drug, the patient had passed about 30 ounces of urine a day, and had had a daily evacuation of the bowels as the result of enema or saline catharsis. There was no previous vomiting, and the pulse ranged from 80 to 90. The wound was slightly infected, and the temperature ranged from 100 to 101.8. The infusion was given because of postoperative sepsis of mild type. Eight hours after the infusion, the patient vomited, and the pulse became irregular and weak. The vomiting was repeated several times during the first twenty-four hours. The secretion of urine was interfered with from the start, and about 2 ounces were secreted during this period. During the second twenty-four hours, $2\frac{1}{2}$ drams of urine were obtained by catheter, and the bowels began to move involuntarily and continuously. The pulse was irregular and weak, the rate about 120 and the breathing was labored. The involuntary stools continued, and became bloody and full of mucus. Nine drams of urine were drawn by catheter during the day.

The following thirty-six hours presented the same symptoms of a severe colitis, and an almost total suppression of urine, and the patient died in extreme exhaustion five and one-half days after the infusion, without improvement in the colitis or the urinary symptoms. There was marked mental distress, but none of the ordinary symptoms of uremia.

A necropsy was held in this case, and its true etiology was first discovered by the microscopic appearance of the kidneys. The essential findings of the postmortem examination were as follows:

The heart was normal. The lungs showed some congestion and edema of lower lobes. There were large masses of clotted blood in the gastrohepatic ligament, the gastocolic and the gastrosplenic ligament, and in the lesser peritoneal cavity. The gallbladder had been removed at the laparotomy. The liver was very friable and deeply bile stained. The bile ducts were much thickened and dilated, and contained many small black calculi. In the common duct there was a stone about 6 mm in diameter. The spleen showed nothing special. The kidneys were very large and deeply jaundiced, there were several cysts on the surface. The capsule stripped with some difficulty, leaving the surface roughish. On section, the kidneys were very edematous and showed evidence of acute degeneration, the color was pale yellow with small hemorrhagic spots. The mucous membrane of the stomach was very much swollen, very red and covered with a layer of thick mucus. The intestines were filled with blackish watery feces, mixed with a large amount of mucus. The descending portion of the colon and sigmoid were covered with membrane and deeply congested. The lesion was most severe in the sigmoid. The glands were normal.

The anatomic diagnosis was fixed as: hemorrhage into the lesser peritoneal sac and gastric ligaments, chronic diffuse nephritis with acute degeneration, general jaundice, biliary calculi in bile ducts.

The microscopic examination of the organs showed biliary pigmentation in the liver cells and bile capillaries, and also in the kidney cells. The kidneys showed an extensive parenchymatous degeneration and calcification of the walls of the convoluted tubules, with large casts which are still present in the tubules. There is a small amount of connective tissue between the tubules. The glomeruli show no important lesions. These changes in the kidney are those characteristic of poisoning by mercuric chlorid.

In the cases of poisoning caused by swallowing the drug, the symptoms begin promptly after it is taken. Abdominal distress and pain at first in the epigastrium and later more general, are the primary symptoms. Nausea and vomiting of the stomach contents and later of mucus, which is more or less blood stained, accompanies the pains. This gastritis is usually promptly treated with egg albumin or milk and lavage, and yields quite readily to such treatment, so that the patient is comparatively comfortable after thirty-six hours' rest and abstinence from food. The mouth shows signs of a mercurial stomatitis in about twenty-four hours, but this rarely is so severe as usually accompanies salivation from calomel. If the poisoning is left to run its course uninfluenced, the patient's attention is called to the diminishing amounts of urine in from forty-eight to seventy-two hours after taking the drug. This may develop to a complete anuria, and the patient dies without restoration of the secreting power of the kidneys. When this occurs, the patient may remain free from cerebral symptoms for the better part of a week, until a terminal form of low delirium supervenes and a weakening heart action proves fatal. There are none of the regular evidences of uremia, and convulsive seizures do not occur. If the kidney condition is survived and its function

reestablished, and in those cases which do not develop this extreme degree of nephritis, there is apt to be a membranous colitis with deep ulcerations and hemorrhages, which may develop and prove fatal even after several weeks have elapsed from the time of the original poisoning

In a case recently observed by one of us in consultation outside the hospital, a patient, who denied having taken the drug, had been anuric for three days. Calculus anuria was suspected, but an examination by Roentgen ray showed no stone, and examination of a stool revealed the presence of mercury. Free colonic irrigations were begun, and after five days of anuria, the patient passed 1 dram, on the following day 5 drams, and then the daily amount slowly rose until, after about a week or ten days of reestablished urination, he was passing over 50 ounces of urine. Notwithstanding this, at about the end of three weeks, he developed a severe colitis, with the passage of large casts of the colon, and died, after a large intestinal hemorrhage.

The therapeutics of mercuric chlorid poisoning up to the present have been quite unsatisfactory. The patients have regularly developed anuria on or about the fourth day after taking the poison, and progress to subsequent death, from lesions of the liver and colon, with or without the reestablishment of the urinary secretion.

Radical procedures have been tried in such cases, including the surgical manipulations of loosening the kidney capsule, but it may well be doubted if such operative treatment has had any specific influence on the course of the clinical picture. The following treatment has been gradually formulated as the result of caring for ten consecutive cases of varying severity which have all resulted in a cure. The first two cases of poisoning resulted from the insertion of two tablets (15 grains) into the vagina, and was treated by favoring the elimination of the poison by frequent and prolonged colonic irrigations with normal saline and by such local measures as were needed to allay the severe vaginitis.

The remaining cases were due to swallowing one or more of the commonly used tablets containing $7\frac{1}{2}$ grains of mercuric chlorid. The treatment in the detail now used at St. Luke's Hospital as a routine has been elaborated through the help of the method of Vogel,¹ by which mercury is readily detected in stomach contents, urine and stools. By this procedure one can determine not only the diagnosis and the necessity of beginning treatment, but also, in some cases, the length of time treatment should be continued. A certain number of

¹ Vogel, K. M., and Lee, O. I. Detection of Mercury in the Excretions. Jour. Am. Med. Assn., 1914, LVII, 532.

patients are brought to institutions either pretending to have taken mercuric chlorid, or fearing that they have taken it by mistake in the dark, etc. It is particularly important to know if a patient has not taken the poison, for the treatment is most irksome to the patient, and entails unusual activity on the part of the nursing department.

Vogel's method consists of separating the mercury from its albuminous combinations in the organic material to be examined and then subliming it in a sealed tube to form an amalgam on a small piece of dentist's gold. Dr. Vogel states that

If mercury is present it will manifest itself by the appearance of a silvery patch of amalgam on the gold foil. If the amount of the metal is exceedingly minute there will be simply a pale discoloration of the gold, seen to better advantage with the hand-lens or by removing the pellet from the tube and examining it with the low power of the microscope, but if the amount is larger the deposit on the gold will be very easy to recognize.

Before outlining the treatment, attention is directed to some characteristics of these cases which have been treated by us and studied by Vogel's method of detecting mercury in excreta.

In the first place, it has been found that mercury, in cases of mercuric chlorid poisoning, is regularly found in the stomach for several days after the ingestion of the poison. That it is not wholly swallowed in the saliva but is secreted by the stomach in an effort to eliminate it from the body, and that it is not part of the poison held in combination with the mucous membrane of the stomach, seem to be indicated by the fact that after several days the tests are negative, to become positive again before all the mercury is eliminated. This corresponds to the behavior of the tests conducted on urine and feces, late in the poisoning. Certain experiments are given below which indicate the same thing.

Another feature which is a determining factor in the length of time treatment should be carried on is the behavior of the mercury elimination after the patients, apparently, are entirely recovered. A reference to the summaries of the tests for mercury under the case histories will show the very long time it takes to free the system of mercury after mercuric chlorid poisoning. In Case 6, in which nephritis existed before the poisoning, in Case 7, in which successive doses were taken, and in Case 8, in which a large dose was taken, the excretion of mercury by the kidneys, the colon and the stomach lasted for days after all symptoms had cleared up. It has become quite apparent that treatment need not be kept up after the urine, and particularly the stools, begin to show negative results.

The treatment, as it is formulated at present for cases coming under observation early, is as follows. The first indication is to give the patient the whites of several eggs and then to wash out the stomach thoroughly. This has usually been done before the patients are admitted to the hospital. On admission, the stomach contents are expressed and examined for mercury, the stomach is thoroughly washed, and a pint of milk introduced. If no stomach contents are obtained before lavage, then the lavage water is examined for mercury. Urine passed spontaneously, or that obtained by catheter, is examined for mercury. The metal appears in the urine in from three to twenty-four hours after it has been swallowed. If more than a day has elapsed since the poisoning occurred, a stool should also be examined for the poison. If the first lavage does not allay the nausea and vomiting, it is repeated after an hour, and the following routine is begun as soon as the stomach will permit.

- 1 The patient is given every other hour 8 ounces of the following mixture: Potassium bitartrate, 1 dram, sugar, 1 dram, lactose, one-half ounce, lemon juice, 1 ounce, boiled water, 16 ounces. Eight ounces of milk are administered every alternate hour.

- 2 The drop method of rectal irrigation with a solution of potassium acetate, a dram to the pint, is given continuously. The amounts of urine secreted under this treatment are very large. In Case 8, 269 ounces were passed in twenty-four hours on the fourteenth day of treatment.

- 3 The stomach is washed out twice daily.

- 4 The colon is irrigated twice daily, in order to wash out whatever poison has been eliminated in that way.

- 5 The patient is given a daily sweat in a hot pack.

It is imperative to emphasize the necessity of keeping up the treatment with the colonic drip enteroclysis day and night without interruption. It entails discomfort for the patient, but the victims of accidental poisoning are always willing to do anything to recover from their plight, and the attempted suicide usually repents rapidly of his error, and the hope of his life being saved stimulates his patience and desire to cooperate.

In cases in which one single dose has been taken, after two negative examinations of the urine, on successive days, it seems legitimate to stop the treatment. In the fifth case, the urine was found to contain no mercury on at least two examinations before discharge. In view of the behavior of subsequent cases, which have been more thoroughly studied, it is probable that this patient excreted mercury for some time after leaving the hospital. For the less severe cases, a week

may be a sufficient time for treatment. When large or successive doses have been taken, or when there is a preexisting kidney lesion, or when treatment begins several days after the poison is taken, longer periods of treatment, up to three weeks, are necessary.

It is interesting to consider how much damage the kidney suffers as a result of eliminating, even in a highly diluted form, an amount of mercury which hitherto in medical experience has led to fatal results. That such damage is not always great is indicated by the fact that in Case 5, 76 per cent of phenolsulphonephthalein was excreted in two hours, the second day that the man's urine was free from mercury. In Case 3, the phenolsulphonephthalein excretion was 55 per cent. Six weeks after discharge the patient was apparently free from sequelae of her poisoning.

With one exception all these cases came under treatment within twenty-four hours of taking the poison. In cases which have reached the stage of anuria, however, favorable results cannot always be expected. While it is perfectly possible to reestablish urination, the cases quite regularly go on to a fatal termination, with degenerative liver changes, and a colitis of the so-called diphtheritic type. In one of the present cases, Case 6, in which there was preexisting nephritis, the urinary output was reduced to 32 minims in twenty-four hours on the fifth day after taking the drug in spite of the fact that treatment was begun three hours after the poisoning. Recovery resulted, but the treatment was much longer than usual. Two of the patients were in the hospital over six weeks and gave positive Wassermann reactions, which were entirely unaffected by the poisoning.

Under the treatment detailed above, these patients quiet down to their routine and, as a rule, do not suffer except from the discomforts of the therapeutic measures. The stomach becomes tolerant of the milk diet and the alkaline drink after from twenty-four to thirty-six hours. The kidney secretion at first is excessive, and may run up to 130 or more ounces in the twenty-four hours. This usually diminishes in spite of the continued exhibition of fluid between the fifth to the tenth day, and may nearly stop altogether, as in Case 6. It is at this period that the continuous water cure and the rest in bed must be insisted on. If this period is successfully passed, the secretion of urine again increases often to a higher level than at first. The mercury itself seems to act as a diuretic at this stage of the treatment. The bowels usually show some irritation, but when the treatment is faithfully carried out, the tendency to diarrhea and colitis is regularly controlled by the colonic irrigations, and other medication for this symptom has been rarely necessary.

In order to clear up some of the toxicologic points which have been raised by the study of these cases, Professor Lieb has carried out the following experiments in the pharmacology laboratory at the College of Physicians and Surgeons. Several animals were operated on under narcosis, and after the esophagus had been tied off so that no connection was left between the pharynx and the stomach, a hypodermic dose of mercuric chlorid was given. The excretion of the poison was then studied by the Vogel method. Three series of experiments were done. In Series 1, two rabbits were used. After the preliminary operation each received 20 mg of mercuric chlorid hypodermically. After a few hours, mercury was found in the contents of the stomach and in that of the colon of both animals. In Series 2, three decerebrated cats were employed and prepared in the same way as given above. The presence of mercury was demonstrated in two of these animals in the urine and feces, and also in the stomachs after from four to eight hours. In Series 3, five decerebrated cats were again experimented on, and both the esophagus and the duodenum were tied off. From 15 to 20 mg were injected into the jugular vein. Three cats gave a positive reaction after from six to eight hours. Another line of investigation concerning the elimination of mercury was made in the wards. Two patients who needed hot packs were receiving weekly hypodermic doses of mercuric salicylate. In both cases pads of filter paper were placed on the skin of the axilla, and after being saturated in the sweat of the patients, reacted positively to the Vogel test for mercury.

CASE 1—Admitted December 8. Three days before admission, patient had inserted two 7½-grain mercuric chlorid tablets in the vagina to relieve pain in the lower abdomen. Soon afterward she began to have severe abdominal pain, and her mouth became sore and salivated. She had vomited four times before admission.

The patient appeared ill and uncomfortable, the mouth was foul, with sordes on teeth and gums, tongue was badly coated, there was moderate salivation, tonsils and pharynx were congested, and the parotid gland on each side was swollen and tender. In the vagina there were yellow and dark brown sloughs on the inner side of each labium major, also yellow and white sloughs on both sides of vagina. The cervix was red and swollen, and there was a watery discharge from the os uteri.

December 9, saline douche was ordered twice daily, and gastric lavage was given, followed by castor oil, through the tube. Colon irrigation (4 gallons) was repeated twice daily.

December 23, patient's condition had decidedly improved in last few days, mouth was much cleaner, she still had a vaginal discharge. Patient left hospital against advice, and was reported well three years later.

EXTRACT FROM URINE CHART, CASE 1

Date	Amount, cc	Reaction	Sp Gr	Albumin	Sugar	Microscopic
Dec 9	720	Acid		Trace	0	Many red blood cells
Dec 10	840	Acid		0	0	No blood (catheterized)
Dec 11	500	Acid	1 030	Trace	0	Urates, no casts found
Dec 12	510	Acid		Trace	0	Pus cloud
Dec 13	750	Acid	1 036	Trace	0	Pus sediment
Dec 14	840					
Dec 15	540	Acid	1 030	Trace	0	Pus cloud
Dec 16	420	Acid	1 030	Trace	0	Pus and blood sediment
Dec 17	660	Acid			0	Pus and blood sediment
Dec 18	540	Acid	1 014	Trace	0	Pus cloud
Dec 19	420	Alkaline	1 035	Trace	0	Pus cloud
Dec 20	420	Acid		Trace	0	Few leukocytes and ep cells
Dec 21	960	Alkaline	1 026	Faint trace	0	Hyaline casts

CASE 2—Admitted November 21 On the morning of the day of admission at 2 a m, patient had inserted one 7½-grain mercuric chlorid tablet in vagina to avoid conception Soon afterward she had severe burning sensation in the region and attempted douching, without success Realizing the gravity of the situation, she came to the hospital, complaining less of pain in the vagina, than peculiar paresthesia and cramplike pains in hands and feet No salivation was evident

Physical examination was negative, except for a good deal of redness of vulva, with seropurulent discharge from vagina Mucous membrane of vagina was covered with a white slough Cervix was red

Treatment was ordered as follows an alkaline douche twice daily, forced fluid diet, a saline colon irrigation twice daily The patient was discharged from the hospital at the end of a week

EXTRACT FROM URINE CHART, CASE 2

Date	Amount, cc	Reaction	Sp Gr	Albumin	Sugar	Microscopic
Nov 21	1,620	Acid	1 008	Faint trace	0	Many leukocytes, no casts
Nov 22	3,390	Alkaline	1 006	Faint trace	0	Few hyaline casts
Nov 23	4 320	Alkaline	1 008	Faint trace	0	Few hyaline casts
Nov 24	3,990	Alkaline	1 008	Faint trace	0	Few hyaline casts
Nov 25	4,920	Alkaline	1 014	Faint trace	0	

CASE 3—Admitted February 12 Twenty-four hours previously she had swallowed three 7½-grain mercuric chlorid tablets in mistake for soda mints Immediately she drank milk mixed with eggs, and a doctor arriving half an hour later washed out her stomach She began to vomit soon after taking tablets but this was relieved by the lavage Six hours ago she began to have epigastric pain and abdominal cramps, accompanied by diarrhea Urine was scanty and she had headache and sore throat

EXTRACT FROM URINE CHART, CASE 3

Date	Amount, c c	Reaction	Sp Gr	Albumin	Sugar	Microscopic
Feb 12	180	Acid	1 025	Marked trace	0	Few hyaline casts
Feb 13	750	Neutral	1 022	Marked trace	0	Hyaline and gran casts
Feb 14	2,450	Alkaline	1 019	Marked trace	0	Hyaline and gran casts
Feb 15	1,500	Alkaline	1 013	Marked trace	0	Pus cloud
Feb 16	400	Acid	1 022	Marked trace		Hyaline and gran casts
Feb 17	925	Neutral	1 021	Faint trace	+	Hyaline casts
Feb 18	600	Alkaline	1 013	Faint trace		Hyaline casts
Feb 19	900	Neutral	1 013	Faint trace		Leukocytes
Feb 20	900	Neutral	1 016	Faint trace	0	Leukocytes
Feb 21	950	Alkaline	1 017	Faint trace	0	Leukocytes
Feb 22	1,800	Acid	1 011	Faint trace	0	Leukocytes
Feb 23	1,500	Acid	1 012	Faint trace	0	Pus cloud
Feb 24	2,400	Acid	1 014	Faint trace	0	Pus cloud
Feb 25	800	Alkaline	1 015	Faint trace	0	Pus cloud
Feb 26	400	Acid	1 012	Faint trace	0	Leukocytes
Feb 27	550	Acid	1 015	Faint trace	0	Leukocytes
Feb 28	425	Alkaline	1 016	Faint trace	0	Leukocytes

Phenolsulphonephthalein excretion, February 12, 51 per cent

Phenolsulphonephthalein excretion, February 28, 55 per cent

Physical examination was negative, except for general abdominal tenderness, most intense over lower half

On admission the patient was put on a continuous rectal irrigation by the drop method, containing potassium acetate 1 dram to the pint. This was continued from February 12 to 17, patient then complained of soreness about rectum, and of the proctoclysis making her very nervous. She was then given a colon irrigation each day for four days, when the proctoclysis was again started, and continued until discharge. Hot packs were given daily while the patient was in the hospital. The lumbar region over the kidneys was cupped every three hours during the first three days she was in the hospital.

Patient left the hospital, February 28, in very good general condition, and although advised to remain in hospital until urine was clear of albumin, she left against advice.

CASE 4—Admitted November 11. On night of admission, patient took two $7\frac{1}{2}$ -grain mercuric chlorid tablets. She arrived in the hospital in less than an hour, where stomach was washed. Past history was negative, except that one year before this she was treated for two months for "kidney trouble."

Physical examination revealed the right kidney distinctly palpable, but otherwise was negative.

November 11, mercury present in both vomitus and urine.

November 12, treatment was started on continuous rectal irrigation by the drop method, containing potassium acetate one-half ounce to quart of water.

November 18, patient left the hospital cured, although no examination for mercury was noted at time of discharge.

CASE 5—Admitted January 23. About one hour before admission patient took two tablets which he thought were headache medicine. Ten minutes later he had burning pain in stomach and took a glass of milk which gave slight

EXTRACT FROM URINE CHART, CASE 4

Date	Amount, c c	Reaction	Sp Gr	Albumin	Sugar	Microscopic
Nov 11		Acid	1 015	Trace	0	Many hyaline casts
Nov 12	1,770					No blood, no casts
Nov 13	2,440	Acid	1 005	0	0	Few leukocytes
Nov 14	4,070	Acid	1 005	0	0	Few leukocytes
Nov 15	4,320	Acid	1 010	0	0	Few leukocytes
Nov 16	3,630	Alkaline	1 010	Trace	0	Few leukocytes
Nov 17	1,340	Alkaline	1 010	0	0	Few leukocytes
Nov 18		Acid	1 005	0	0	Few leukocytes

relief The pain continued, and he came to hospital He vomited in examining room and was given a gastric lavage (both of which proved to contain mercury) Patient brought a tablet of the medicine with him, which proved to be the ordinary 7½-grain tablet of mercuric chlorid On being sent to ward, he was given another gastric lavage lasting fifteen minutes, then drank one pint of milk, one-half hour later the stomach was again washed clean (this is the lavage reported January 24 as containing mercury) He was put on milk diet, continuous proctoclysis (drop method) with potassium acetate, 1 dram to pint of water Potassium bitartrate solution, 8 ounces, was ordered every hour Patient was discharged, January 31

EXTRACT FROM URINE CHART, CASE 5

Date	Amount, c c	Reaction	Sp Gr	Albumin	Sugar	Microscopic
Jan 23	2,550		1 008	Very faint trace	0	Few leukocytes and ap cells
Jan 25	2,200	Neutral	1 010	Faint trace	0	Few leukocytes and ap cells
Jan 26	3,100	Neutral	1 008	Faint trace	0	Many leukocytes and triple phos crystals
Jan 27	3,900	Alkaline	1 010	Faint trace	0	Few leukocytes and ap cells
Jan 28	1 025	Neutral	1 010	Very faint trace	0	Few leukocytes
Jan 29	1,950	Alkaline	1 010	Faint trace	0	Few leukocytes and ap cells
Jan 30	2,350	Neutral	1 010	Faint trace	0	Few leukocytes and ap cells
Jan 31	600	Acid	1 020	Very faint trace	0	Few leukocytes and ap cells

January 29, phenolsulphonephthalein test, first hour, 50 per cent, second hour, 26.5 per cent, total, 76.5 per cent

SUMMARY OF TESTS FOR MERCURY, CASE 5

	Jan 23	Jan 24	Jan 25	Jan 26	Jan 27	Jan 28	Jan 29
Urine	Positive	Positive	Positive	Positive	Positive	Negative	Negative
Vomit	Positive						
Lavage	Positive	Positive					
Stool	-	Positive	Positive				

CASE 6—Admitted March 26, at 5 45 p m At 3 p m, patient took four 7½-grain mercuric chlorid tablets Shortly after this she took some castor oil and mustard water which made her vomit At 4 o'clock she was seen by a physician who gave her a thorough gastric lavage and some milk

The past history of the patient revealed that she had had an interstitial keratitis and was given two doses of salvarsan and a prolonged mercurial treatment One other sister had congenital syphilis The Wassermann reaction is said to be positive in both her sister and herself

Physical examination was unimportant The routine treatment as outlined in this article was carried out beginning March 26 and continued for more than five weeks March 26, the vomitus and lavage water were both positive for mercury The stools, the urine and the gastric lavage were positive to the mercury tests for a period of several weeks March 28, the first negative test occurred in the gastric lavage May 2, the first negative test was found in the urine May 16, the stool was negative for the first time The mercury was not completely eliminated by July 3 and occasional positive results were found up to that date, when the examinations were stopped

EXTRACT FROM URINE CHART, CASE 6

Date	Amount, c c	Reaction	Sp Gr	Albumin	Sugar	Microscopic
Mar 27	39½	Acid	1 010	Faint trace	0	Hyaline and gran casts
Mar 28	137					
Mar 29	45					
Mar 30	45					
Mar 31	?					
Apr 1	55					
Apr 2	8½					
Apr 3	8½					
Apr 6	1,46½	Neutral	1 010	Faint trace	0	Few leukocytes, hyaline casts
Apr 11	660	Alkaline	1 015	Marked trace	0	Few leukocytes
Apr 13	1,310	Neutral	1 010	Trace	0	Pus cells
Apr 30	3,991	Alkaline	1 002	Very faint trace	0	Few leukocytes
May 10	4,640	Neutral	1 005	Very faint trace		Few leukocytes

The striking feature in this case is that on March 31 there was an almost complete suppression, and when the twenty-four-hour secretion was only 32 minims March 26, the Wassermann reaction was double plus, and on April 24 it was four plus

The phenolsulphonephthalein excretion in two hours was as follows April 7, 33 per cent, April 9, 4 per cent, April 17, 41 per cent, April 23, 47 5 per cent, May 10, 71 4 per cent

CASE 7—Admitted April 9 Four days ago patient took one 7½-grain mercuric chlorid tablet The only symptom complained of is that she vomited a little later Twenty-four hours ago, she took two more 7½-grain tablets, and about an hour later had pain in the abdomen for which she took some "soda" After this she vomited several times About 3 o'clock this afternoon, she swallowed another 7½-grain mercuric chlorid tablet, and vomited about half an hour later The bowels have moved several times a day for the last few days, but she has felt fairly well since taking the first tablet except for a

burning sensation in abdomen, and headache, and has had no appetite. She has noticed no decrease in amount, or change in character of urine.

Physical examination was unimportant. The routine treatment was given and continued for two months although the symptoms of poisoning were practically absent after the first days of gastric irritation. The tests for mercury were positive for many days both in the urine and the stools and the gastric lavage. The first negative examination in the urine was on April 27, and in the feces on June 8. But the mercury was not completely eliminated by July 3. Occasional positive results were obtained up to that date, when the examinations were stopped.

EXTRACT FROM URINE CHART, CASE 7

Date	Amount, cc	Reaction	Sp Gr	Albumin	Sugar	Microscope
Apr 10	1,175	Acid	1 010	Faint trace	0	Many leukocytes
Apr 12	600	Alkaline	1 010	Very faint trace	0	Many leukocytes
Apr 13	1,600	Neutral	1 015	Faint trace	0	Many leukocytes, mucus
Apr 17	3,500	Alkaline	1 005	Trace	0	Many leukocytes
Apr 30		Alkaline	1 010	Very faint trace	0	Few leukocytes
May 10		Neutral	1 015	Very faint trace	0	Many leukocytes
May 20	1,500	Neutral	1 010	Faint trace	0	Many leukocytes
May 22		Neutral	1 010	Trace	0	Many leukocytes
June 7		Acid	1 005	Very faint trace	0	Many leukocytes
June 22		Neutral	1 005	Faint trace	0	Many leukocytes
June 23	1,800	Neutral	1 015	Trace	0	Few leukocytes
June 28		Alkaline	1 005	Trace	0	Few leukocytes
July 1		Acid	1 015	Trace	0	Few leukocytes

The phenolsulphonaphthalein excreted in two hours was as follows: April 9, 66.5 per cent; April 21, 62.5 per cent; June 22, 65 per cent.

CASE 8—Admitted June 14. About an hour and a half before admission to the hospital, patient took by mistake six 7½-grain mercuric chlorid tablets, dissolved in water, in mistake for a sleeping mixture. She drank a glass and a half of water after this. In a few minutes she felt great discomfort in her throat, and vomited a large amount. She was given three raw eggs, a doctor was called and she was sent to the hospital. Her physical examination was negative. The symptoms need not be given here. The routine treatment was instituted.

June 14, the urine was positive to the mercury test, but the gastric lavage on admission was twice negative. It became positive on the 15th, and remained so until the 17th, after which it was negative. June 23, the urine was negative for the first time, and on July 20 the first negative stool was examined. The elimination of mercury was not complete at time of discharge, July 28.

CASE 9—Admitted July 11. About three hours before admission, patient took one 7½-grain tablet of mercuric chlorid by mistake for aspirin. He went to a doctor's office immediately and in about fifteen minutes was given mustard and vomited several times. The stomach was then washed out thoroughly and patient drank milk. After that he was sent to the hospital. Distress in abdomen followed the lavage, but there was no actual pain. The bowels were regular, the urination was normal, the appetite good.

Physical examination was negative and the routine treatment was begun July 11, the urine, stool, vomitus and lavage were all positive to mercury July 24, the first negative urine was found, but there were no negative stools before leaving the hospital

EXTRACT FROM URINE CHART, CASE 8

Date	Amount, c c	Reaction	Sp Gr	Albumin	Sugar	Microscopic
June 14	1,098	Alkaline	1 025	Very faint trace	0	Mucus
June 16	2,650	Alkaline	1 005	Very faint trace	0	Many leukocytes
June 22	5,667	Neutral	1 005	Faint trace	0	Few leukocytes
June 24	4,692	Alkaline	1 005	Very faint trace	0	Few leukocytes
June 28	3,196	Alkaline	1 010	0	0	Few leukocytes
July 1		Alkaline	1 016	Trace	0	Few leukocytes, hyaline and gran casts
July 4	5,911	Alkaline	1 005	0	0	Few leukocytes
July 6	6,764	Alkaline	1 005	Faint trace	0	Few leukocytes
July 9		Alkaline	1 020	Very faint trace	0	Few leukocytes
July 11	5,484	Alkaline	1 005	0	0	Few leukocytes
July 14		Alkaline	1 005	0	0	Few leukocytes
July 17	4,916	Alkaline	1 010	0	0	Few leukocytes
July 19	4,052	Alkaline	1 005	0	0	Few leukocytes
July 23		Alkaline	1 005	Faint trace	0	Few leukocytes

June 14, the phenolsulphonephthalein excretion in two hours was 55.5 per cent, and on July 14, it was 45.7 per cent July 14, the Wassermann reaction was two plus in spite of the excessive dose of the mercury

EXTRACT FROM URINE CHART, CASE 9

Date	Amount, c c	Reaction	Sp Gr	Albumin	Sugar	Microscopic
July 11	1,950	Acid	1 010	Very faint trace	0	Few ep cells, hyaline casts
July 12	3,930	Neutral	1 005	Faint trace	0	Few ep cells, hyaline casts
July 13	3,656	Neutral	1 005	0	0	gran casts Epithelium
July 14	4,204	Acid	1 010	Very faint trace	0	Epithelium
July 15	2,833	Acid	1 015	Very faint trace	0	Epithelium
July 16	3,900	Acid	1 010	Very faint trace	0	Epithelium
July 17	3,929	Acid	1 013	Faint trace	0	Epithelium
July 18	4,288	Acid	1 010	Faint trace	0	Epithelium, occasional gran cast
July 19	2,986	Neutral	1 005	Very faint trace	0	Epithelium and mucus
July 20	4,022	Neutral	1 005	Very faint trace	0	Epithelium and mucus
July 21	2,376	Neutral	1 005	Very faint trace	0	Epithelium and mucus and leukocytes
July 23	3,636	Neutral	1 005	Very faint trace	0	Epithelium and mucus and leukocytes
July 24		Alkaline	1 020	Faint trace		Epithelium and mucus and leukocytes

July 24, phenolsulphonephthalein test showed 55.8 per cent excretion in two hours

EXTRACT FROM URINE CHART, CASE 10

Date	Amount, cc	Reaction	Sp Gr	Albumin	Sugar	Microscopic
Mar 22	2,737	Acid	1 025	Faint trace	0	Pus cloud
Mar 24	3,107	Alkaline	1 010	Faint trace	0	Many leukocytes
Mar 26	3,107	Alkaline	1 010	Very faint trace	0	Occasional gran east
Mar 30	3,778	Acid	1 010	Very faint trace	0	No casts

CASE 10—Admitted March 21 Patient took by mistake three tablets of mercuric chlorid dissolved in 6 ounces of water, as a gargle, and swallowed practically all of it She vomited fifteen minutes later a greenish fluid Pain in the epigastrium followed immediately, and patient came at once to the hospital where she vomited again, a thick, foamy, colorless mucus The patient came under treatment within an hour after poisoning There were no symptoms after the first two days, and the treatment was routine She was discharged March 31 All the excreta and stomach washings were positive to mercury for three days The stomach washing was first negative on March 24, to be again positive March 27 The urine was first negative on March 24 and positive at intervals until treatment ceased, March 31 The colon irrigations were positive until March 30

130 East Thirty-Fifth Street—130 East Sixty-Second Street

THE COAGULATION TEST FOR SYPHILIS, AS DEVISED BY HIRSCHFELD AND KLINGER *

HAROLD NEWTON COLE, M D

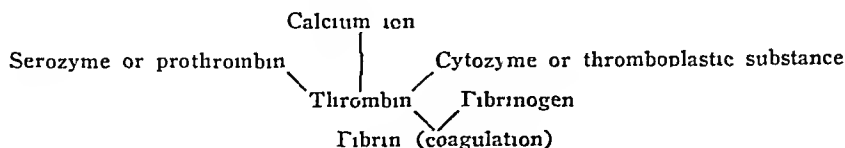
AND

SAMUEL ENG-KIU CHIU, M D

CLEVELAND

Since the first appearance of the Wassermann test for syphilis, many short cuts and modifications have been devised or suggested and, we regret to say, most of them have failed to stand the test of time as well as the original. Moreover, several entirely new methods of diagnosis have been devised, of which Noguchi's cutaneous test has probably come the closest to being satisfactory, and that only in certain stages of the disease. In 1914, Hirschfeld and Klinger reported to the Congress of Internal Medicine at Wiesbaden that they had succeeded, by means of the process of coagulation, in distinguishing a syphilitic from a nonsyphilitic serum. At that time they had examined about 250 serums, they later reported that about 500 had been tested by a collaborator, and since then, in a personal communication, have written that around 1,000 successful tests have been made. During the past nine months, we have also been working with the technic, and have now done about 600 tests which we wish to report.

The reaction is based on the phenomena of coagulation of the blood. Hirschfeld and Klinger conceived the idea that there might be possibly a deviation of the cytozyme, akin to the deviation of the complement in the Wassermann reaction. To understand the details, it will be necessary to recall several of the principles of coagulation of the blood, and as Hirschfeld and Klinger have worked entirely on the schema as given by Bordet and Delange, we will only mention the work of these authors—it being outside the scope of this paper to discuss coagulation of the blood in its entirety. According to this schema, as we can see, coagulation is due to the precipitation of the fibrinogen of the plasma by the thrombin.



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The thrombin itself is the product of three factors first serozyme, an albuminoid thermostabile substance contained in the plasma, second cytozyme, a thermostabile substance, lipoid in nature, derived from tissues of the body, blood cells, platelets, etc., and very similar to lecithin and cephalin, third, calcium in the state of ionization (the non-ionized salts, for example, citrate, Arthus, Sabbatini and others have shown to be not active) The thrombin forms itself only in the presence of calcium, only a few seconds of time being required, and, once formed, it provokes coagulation of the fibrinogen, even in the absence of the ionized calcium salts Bordet and Delange have shown that 1/1,000 or 1/20,000 mg of the dried alcoholic extract of muscle or platelets forms thrombin capable of coagulating 0.5 c.c. of oxalate plasma

Bordet and Delange entirely separate the two phases of coagulation The first phase consists in the formation of thrombin by the interaction of serozyme and cytozyme in an ionized calcium medium The solution of sodium oxalate precipitates the calcium salt in the plasma and thus causes the decalcification of the mediums The coagulation is produced by the action of the thrombin formed in the first phase on the plasma (fibrinogen) added at the same time as the sodium oxalate solution (second phase) The separation of the two phases allows one to measure the quantity of thrombin formed in a given unit of time The more thrombin there is in the solution, the quicker is the coagulation Another advantage of their method consists in the employment of relatively pure solution They take the blood in a paraffined tube containing a solution of sodium oxalate The blood remains liquid, and after prolonged and speedy centrifugalization furnishes a plasma that is almost free from cytozyme By recalcification the plasma is coagulated, and after the clot is expressed one obtains a serum rich in serozyme containing only traces of cytozyme For cytozyme, Bordet and Delange use an extract of platelets or of organs, pure and sufficiently concentrated To determine the strength of a substance in cytozyme, one proceeds in the following manner The solution is treated with serozyme in calcified solution for fifteen minutes Then the oxalate plasma is added The time which elapses between the addition of the plasma and the beginning of the coagulation is inversely proportional to the amount of thrombin formed If the plasma remains liquid, one concludes that the medium contains no thrombin

Hirschfeld and Klinger have noticed the affinity of the cytozyme for the globulin of serum The important rôle played by the globulins in most serologic reactions is a familiar fact These findings have led them to inquire whether the technic of coagulation would not allow

them to discover certain phenomena of immunity. They have accordingly directed their attention especially toward a possible deviation of the cytozyme analogous to the deviation of the complement in the Wassermann reaction.

THE COAGULATION TEST

This reaction is based on the fact that the organ extracts employed in the Wassermann reaction represent very active cytozyme. This property of the cytozyme disappears after contact with a syphilitic serum, while it remains intact after a similar treatment with a normal serum.

In short, one measures the activity of a certain quantity of an extract after mixing it with a serum to be examined. If coagulation is not retarded sensibly and the extract is active in its coagulating power, the serum is normal. If, on the other hand, the coagulation is feeble or completely inhibited, the serum is syphilitic.

DIRECTIONS FOR THE REACTION

1. For serozyme, Bordet and Delange employed the serum of rabbit. Hirschfeld and Klinger have found that sheep's or goat's blood is richer in serozyme than that of the rabbit. These animals have less delicate platelets. They consider that paraffined tubes for receiving blood are not essential, if these vessels are perfectly clean and dry, warmed to 40 C and the blood is drawn by a cannula. The latter authors have found beef blood unsuitable and we have likewise. We prefer paraffined vessels.

PREPARATION OF SEROZYME

A 300-cc flask is filled with 100 cc of water and marked accurately at the fluid level. The flask is sterilized with dry heat to 180 C for half an hour and then coated all over with paraffin. One puts into the flask 10 cc of the 1 per cent sodium oxalate solution and 0.5 cc of 10 per cent sodium chlorid solution for each 100 cc of blood. Mix them well by shaking. Fill with blood to the desired mark and shake it gently but thoroughly. Pour the blood thus prepared into centrifuge tubes heated to 40 C, and speedily centrifugalize it till the cellular elements have settled to the lower half of the tube. Remove the clear plasma with a pipet, taking care not to remove the red cells at the same time. Centrifugalize the clear plasma for a second time for at least thirty minutes to further get rid of the cytozyme present. Plasma thus obtained can be stored for three days in a refrigerator. It should be clear, yellowish in color and free from hemoglobin. This is the oxalate plasma.

FOR SEROZYME OR EXTRACT OF SERUM

To 10 cc of the oxalate plasma thus obtained, add 12 cc of the 1 per cent calcium chlorid solution. Place the mixture in incubator until the clot is firmly formed. Express the clot by means of a pair of broad sterilized forceps. Sometimes it is necessary to repeat the procedure if not entirely clear. Then leave the clear liquid in the incubator for another half hour to destroy the further formation of thrombin. It is well to prepare the serozyme four or five hours before the experiment. Before use, the serozyme thus obtained should be diluted to five times its volume with 0.85 per cent sodium chlorid, and the mixture should stand for one hour.

2 Calcified saline is prepared by mixing 100 cc of 0.85 per cent of sodium chlorid and 5 cc of 1 per cent solution of calcium chlorid. Frankel and Thiele recommended 5 per cent calcium chlorid in physiologic salt solution. We have tried their suggestion and find it does not work. Moreover, it is physiologically impossible, for it is a well-known fact that in strengths above 0.5 per cent calcium solution clotting is impossible.

3 Oxalate plasma is prepared in the proportions given in Table 1

TABLE 1—PREPARATION OF OXALATE PLASMA

Oxalate plasma	20 parts
Solution sodium oxalate, 1 per cent	20 parts
Normal saline	60 parts

This mixture should be prepared just before use

4 For the organ extract, all alcoholic extracts may be used. Merck's preparation of guinea-pig's heart extract, of which 0.1 cc of a dilution of 1:160 causes coagulation after contact with serozyme in three to four minutes, is recommended by Hirschfeld and Klinger. We have prepared even better extracts of our own, both from guinea-pig and from human hearts.

TITRATION OF EXTRACTS

In order to ascertain what doses should be used in the experiment, there is prepared a series of dilutions of extract in 0.85 per cent sodium chlorid solution, doubling each time the quantity of sodium chlorid solution. We recommend the initial dilution of 1:10 strength, to be followed consecutively by 1:20, 1:40, 1:80, 1:160 and 1:240. Mix 0.1 cc of each dilution with 1 cc of calcified saline and 0.5 cc of serozyme diluted one hour before. Let the mixture stand at room temperature for fifteen minutes, and add to it the mixture of oxalate plasma. One selects for the reaction the three consecutive dilutions, of which the first and second coagulate the plasma in from one to two minutes, and the third in from three to four minutes.

PREPARATION OF PATIENT'S SERUMS

In taking patient's blood, great care should be exercised to avoid hemolysis in the specimens to be tested. All serums should be inactivated at 58°C for one hour in order to destroy the cytozyme present in them.

TECHNIC OF THE TEST

It is necessary to state that in order to make the test of diagnostic value, every detail is to be carried out accurately. We refer to the collecting of blood from the animals for experiments. The measurement must be carefully made in the quantity of blood taken and in the reagents used. The time for incubation of serozyme must be exact, and after the process it must be perfectly free from thrombin. Many a time, disappointment invariably follows only a slight overlooking of these seemingly little things. In every reaction, a preliminary titration of extract and control must be carried out before the main reaction is begun. It will be of great help if a preliminary test of one known positive and one known negative is also made. If the titration of extract fails to give a good result—either too rapid or too slow in the coagulation time—correct the fault at once before proceeding to the test proper.

TABLE 2—SCHEMA OF REACTION

Patient's serum, 0.1 cc, heart antigen, 0.1 cc
 Stand for one hour
 Calcified NaCl, 1.0 cc
 Serozyme diluted, 0.5 cc

Stand for fifteen minutes

Diluted oxalate plasma, 10 cc

After the addition of oxalate plasma, observe and record the time of coagulation. With a little practice, a large number of these specimens can be read at one time without difficulty

THE CONTROLS

In order to make sure that the test is properly carried out, a series of controls must be made as follows

The serozyme control consists of a mixture of diluted serozyme (1 5), 0.5 cc, and calcified saline, 1 cc. It should remain perfectly clear and liquid for hours, and show no signs of thrombin formation. This test should precede all others in the reaction.

The serum control (D) is to be carried out at the same time as the test proper with each patient's serum. It contains all the reagents except the extract, and it should remain liquid for at least three hours, it should not coagulate before the reading of all the specimens is completed.

TABLE 3—REACTION AS USED BY HIRSCHFELD AND KLINGLER AND IN OUR LABORATORY, SHOWING A SET OF EXPERIMENTS

	Patient	1 40 Minutes	Dilution of Extract 1 80 Minutes	1 160 Minutes	Serum Without Extract	Result of Test	Wasser- mann Result
1	Surgical	5	8	10	0	—	—
2	Surgical	5	8	10	0	—	—
3	Latent syphilis	8	0	0	0	++	++
4	Interstitial keratitis	9	0	0	0	++	++
5	Lesion on penis, ulcer mollis	5	8	10	0	—	—
6	Latent syphilis	8	0	0	0	++	±
7	Cerebrospinal syphilis (spinal fluid)	8	18†	40†	0	+	—
3	Gastritis	6	8	10	0	—	—
9	Asthma	5	8	11	0	—	—
0	Secondary anemia	5	8	10	0	—	—
1	Influenza	5	8	10	0	—	—
12	Latent syphilis (spinal fluid)	8	15	0	0	++	++
13	Cerebrospinal syphilis (spinal fluid)	10	0	0	0	++	++
14	Cerebrospinal syphilis (spinal fluid)	10	0	0	0	++	++
15	Known positive	7	0	0	0	++	++
16	Known negative‡	4	6	8	0	—	—

* The figures indicate the time necessary for coagulation, 0 = no coagulation after four hours. The extract controls alone coagulated in one, two and three minutes, respectively.

† Feeble

‡ Serozyme alone, 0

The plasma control is to be carried out separately and before the main test is begun. It consists of a mixture of 1 cc of calcified saline, and 0.5 cc of serozyme diluted with 1 cc of diluted oxalate plasma. This mixture should remain in solution indefinitely.

Observe and record the time of coagulation.

After the adding of the oxalate plasma to all the tubes, the contents which are at first colorless and clear become flocculent and cloudy. The negative specimens starting from the first tubes gradually become thickened, gelatinous in consistency, and the coagulation takes place consecutively in from three to ten minutes in all the three tubes. The positive cases, however, remain either undotted for hours in all the tubes or they very feebly and slowly coagulate. The time taken from reading is only of comparative value. There is no absolute standard of the coagulation time. It depends largely on the integrity of the serozyme, the strength of the cytozyme and the condition of the oxalate plasma. One reads, therefore, perhaps from two to eight minutes in one reaction and from ten to twenty-five in another. After a little practice one can judge accurately whether the given specimen is positive or negative by the character of the contents of the tubes. It is to be stated here that serozyme loses much of its power of thrombin formation after twenty-four hours' standing. Whenever possible it should be prepared anew.

COMMENT ON THE TEST

It is difficult to offer an explanation of the reaction. It is not primarily an anticoagulability of the syphilitic serum, because it affects its action only after contact with the organ extract. According to Hirschfeld and Klinger, in their early researches on the globulin of serum, there is a colloidal transformation of serum—a sort of ultra-microscopic precipitation of globulins due to contact with alcoholic extracts. This alteration of globulins probably effects absorption and diminution of the activity of the extract. This phenomenon is also observed, although in a less noticeable manner, with the cytozyme contained normally in the serum. One notices this with some syphilitic serums very rich in cytozyme which coagulate more rapidly in the control tubes and which do not furnish a sure result in the coagulation reaction. In such cases, the coagulation takes place very rapidly (in from two to five minutes) in the control tubes (D), while tubes with increasing doses of extract show retardation more marked in those that contain larger doses of extract. On the contrary a nonsyphilitic serum, rich in cytozyme, shows a coagulation more rapid in tubes containing the extract, while the control is slower, although it finally coagulates.

Hirschfeld and Klinger have found this test superior to the Wassermann in many instances, especially in cases of treated syphilis. Moreover, they have produced positive reaction to the Wassermann test by treating normal serums with emulsions of agar or of microbes, and also by prolonged agitation of diluted normal serums, whereas the coagulation test remained negative.

Their results show that the coagulation test for syphilis is as characteristic as the Wassermann

An aqueous extract (cytozyme), Hirschfeld and Klinge¹ find, has no effect on syphilitic serums. It is evident that the special change which the lipoid extract undergoes with the syphilitic serum cannot be due to anticytozyme, but that the reaction of the syphilitic serum with the lipoid extract leads to absorption of its coagulating powers, as a result of which it (lipoid extract) is less useful as cytozyme, or is even changed in its physical and chemical character

COMPARISON WITH THE WASSERMANN REACTION

Of the 548 cases tested by us, fifty-one specimens are spinal fluids from different individuals. The classification given in Table 4 shows the number of the different diseases examined

TABLE 4—CLASSIFICATION OF CASES

Diseases	No
Infectious diseases, including fevers, pneumonia, rheumatism, arthritis, tonsillitis, etc	15
Congenital syphilis	5
Cerebrospinal syphilis	17
Primary syphilis	23
Secondary syphilis	32
Tertiary syphilis	68
Latent syphilis	84
Treated syphilis	73
General paresis, psychoses, etc	5
Tabes dorsalis	6
Gummas	4
Skin diseases, including acne vulgaris, rosacea, etc	37
Medical cases, including diabetes, anemia, diseases of the respiratory, circulatory and digestive systems, etc	131
Surgical cases	48
Total	548

As all the tests have been run parallel with the Wassermann, comments will be made only on the cases giving different results—either positive with this test and negative with the Wassermann, or vice versa. We employ the original Wassermann technic, using four different antigens for each serum. We use alcoholic human heart antigens reenforced with cholesterol.

Of the 548 cases of blood and spinal fluid examined, fifty-eight cases, or 10.5 per cent, give positive results with the coagulation test and negative results with the Wassermann. The diseases comprising these fifty-eight cases are given in Table 5.

TABLE 5—CASES IN WHICH THE COAGULATION TEST GAVE POSITIVE RESULTS AND THE WASSERMANN NEGATIVE

Latent syphilis	19
Treated syphilis	15
Secondary syphilis (spinal fluids)	2
Tertiary syphilis	11
Primary syphilis	4
Cerebrospinal syphilis	3
General paresis	2
Tabes dorsalis	1
Hodgkin's disease	1
Total	<hr/> 58

It is evident from these figures that the coagulation test is more delicate than the Wassermann. In our series it detects 10.5 per cent more cases of syphilis than the Wassermann. In the latent and treated cases of syphilis, in which the Wassermann has often given negative results, the coagulation test has been positive. The four cases of primary syphilis in this series, in which infection was definite, and the lesions were characteristic of primary syphilis and persistent under local treatment, all gave negative results with the Wassermann, while the coagulation test was positive. Likewise in many tertiary cases the coagulation test was positive, while the Wassermann reaction was negative. In general paresis, tabes dorsalis and the cerebrospinal syphilis quoted above, there was, in most cases, not even a trace of complement deviation with the Wassermann reaction, while they came out positive with the coagulation test. There is one case of Hodgkin's disease not accounted for. On account of the lack of history, we are not able to comment on it.

It must be pointed out here that there are a few cases on our record having positive reaction with the coagulation test and negative with the Wassermann, and we cannot find any justification for such results from the history given. Repetition of the test with fresh reagents is of course highly advisable in these cases. The following cases are on record, and we have since had one or two others. In this, however, the test is probably as fallible as the Wassermann.

- J. P., Hodgkin's disease, coagulation ++, Wassermann ±
 A. S., acne vulgaris, coagulation ++, Wassermann —
 L. W., pityriasis rosea, coagulation ++, Wassermann —

On the other hand, it has been observed from time to time that a few serums react negatively with the coagulation test and positively with the Wassermann. Of the 548 cases, we have three specimens giving persistently negative results with this test and positive with the Wassermann. For example, we have

B A, syphilis, coagulation —, Wassermann ++

L B, spinal fluid, syphilis, coagulation —, Wassermann ++

P, spinal fluid, syphilis, generalized eruption, coagulation —, Wassermann ++

In general, we have found that hemolyzed specimens tend to produce coagulation in all the tubes, regardless of the presence or not of tissue extract

We have so far tested only fifty-one specimens of spinal fluids from different patients. The results have been most gratifying. In quite a few cases the Wassermann has given negative results while the coagulation test has been positive. In fact, of the fifty-one cases, the coagulation test gives eleven more positive than the Wassermann, making a difference of 21 per cent more positives for the coagulation test. The original publication reports unfavorable results with the spinal fluids tested. Our small experience, we believe, allows us to state that the spinal fluid, inactivated at 58 C (136.4 F) for half an hour and used in dose of 0.4 cc, gives good results with this test.

The question arises as to the effect of the age of the serums on this coagulation test. We have tested about 150 serums of different ages and at different times. The time elapsed has been from two weeks to two months in different series of the specimens. The results have been uniformly good. With the exception of specimens showing deterioration, they all stand well for at least four weeks, if kept on ice. When a serum deteriorates, it generally gives a positive reaction. It is safe, therefore, to make a conservative estimate that all serums which have been inactivated at 58 C for one hour can be kept in an ice chest for one week or possibly more without the reaction being affected.

For the purpose of studying the stability of the antibodies in the serum, we have made the following experiments. We have heated a few specimens of serums to 65 C (149 F) for from three quarters of an hour to an hour without generally altering the reaction. A few specimens heated to 70 C (158 F) or over showed a tendency of the negative specimens to become positive.

While the results are encouraging with our work for the past nine months, we would still recommend that all the tests should be done hand in hand with the Wassermann. This is especially important with those who have had little or no experience in serologic work. In the hands of experienced workers, this is unquestionably a more delicate test than the Wassermann, and only further work can show its scope and limitations.

CONCLUSIONS

1 The coagulation test carried out by thoroughly reliable and conscientious workers is quite as specific as, and more delicate than the Wassermann, in cases of treated, latent and cerebrospinal syphilis

2 Syphilitic cases, after prolonged and effective treatment, give negative results with the coagulation test, as with the Wassermann

3 A few primary cases have given a positive result with the coagulation test, while the Wassermann was still negative

4 Spinal fluids, after inactivation for half an hour at 58 C, give good results with the coagulation test, if used in doses of 0.4 c c

Our deepest gratitude is due to Prof G N Stewart for his valuable suggestions and advice in carrying out this work

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BOOK REVIEWS

A TEXTBOOK OF PATHOLOGY For Students of Medicine By J George Adams, M A, M D, LL D, F R S, Professor of Pathology in McGill University, Montreal, and John McCrae, M D, M R C P (London), Lecturer in Pathology and Clinical Medicine in McGill University, formerly Professor of Pathology in the University of Vermont Second edition, enlarged and thoroughly revised Octavo, 878 pages, with 395 engravings and 13 colored plates Cloth, \$5 00, net Lea & Febiger, Publishers, Philadelphia and New York, 1914

It is extremely difficult to arrive at a just estimate of the value of this book. The authors state that, while it is not by any means an abbreviation of Professor Adams's Principles of Pathology, it almost necessarily follows the same general lines of presentation. All who, like the reviewer, read with almost the charm of a novel the author's delightful presentation of general pathology in the first volume of the larger work, will be prepared for the same clear and interesting handling of the large underlying problems of disease. In this they will not be disappointed. They will also remember that the second volume of the previous work revealed by its contrast the predominant interest of the author. The facts of pathological anatomy and histology have not fared better in the present work. In their preface the authors state that "the reader will find that continued emphasis is placed on the reasons underlying pathological conditions, although we trust the facts themselves have not been neglected." After a careful reading of the entire book, the reviewer is forced to the conclusion that their hope has not been fulfilled. Of the 810 pages of text, 399 are devoted to General Pathology, and under "Special and Systemic Pathology" in Part Two, about one-third of the discussion is occupied with physiology, normal and pathological. At the most, one-third of the book, or less than 300 pages, is left for the facts of special pathological anatomy. Such a standard textbook as Ziegler's gives more than one half of its nearly 2000 pages to this aspect of pathology. One must admit that pathology includes the whole of our knowledge of disease, and that our understanding of pathological processes has been vastly widened by the application of physiological and chemical methods to their elucidation. One must also admit that investigations of the causes of disease, especially by bacteriological methods, and of the mechanism of the body's defense against infection, have made strides of late years, which a textbook should reflect. Clinical medicine is also contributing much toward an adequate pathology of the living. Pathological anatomist, physiologist, chemist, bacteriologist, and clinician are all concerned with the same problem, each approaching it from a special point of view and attempting a solution of it by special methods. Pathology includes them all. But this is a textbook intended for students, and in our education of the student it has always been the custom to draw the lines which separate the different avenues of approach to knowledge more sharply than the overlapping of their boundaries might seem to warrant. The reviewer cannot look forward to the time when pathological anatomy will be an outworn science. It will always be necessary for the physician, as Virchow emphasized, to think anatomically. If the pathologist does not teach him to do so, who shall? If "the reasons underlying pathological conditions" were self-evidencing and inescapable, like the deductions of mathematics, then the facts might conceivably be omitted. In the present state of pathology, however, much difference of opinion exists as to these reasons, and a satisfactory presentation of all of the arguments requires, first of all, the clear statement of every one of the facts from which men draw such varying conclusions. Medical students have an inborn preference for theoretical discussion, and a wholly natural aversion to the acquisition

of mere dull facts, and the reviewer feels strongly that this book will fall in quite too well with these natural predilections. Certainly no one can turn to it for detailed and authoritative statements of the known facts about the lesions of disease in any portion of the body. On the other hand, the general discussions of principles are admirable, and calculated both to interest the student and to stimulate him to think. If the book had been entitled *An Introduction to Clinical Medicine* it would have given a much clearer idea of its scope, but on page 187 the authors state that "this is neither a textbook of bacteriology nor a work on clinical medicine." This sentence suggests that they had a lurking fear lest their readers might so construe the book. On page 544 they seem almost to apologize for intruding such tiresome details as pathological histology. In discussing lobar pneumonia, they write "To understand properly how this changes to the so-called *gray hepatisation*, a consideration of the microscopic appearance is necessary."

Certain criticisms in detail are called for. There are many obvious errors due to bad proof-reading, the worst of which are in the Table of Contents of Chapter Two, which does not follow the subsequent divisions in the text and contains such a slip as "Disturbances of the intestinal secretions" for "internal secretions." The discussion of the action of poisons, pages 71 to 75, is very inadequate. Either it should have been omitted, and the reader referred to books on pharmacology, or some notice should have been taken of the existence of the vegetative nervous system, and present knowledge of the pharmacodynamic action of drugs on it. Adrenalin and barium chlorid are put down as drugs acting alike on the unstriated muscle of the vessels. Throughout the discussions, both of immunity and of the internal secretions, a strong impression is created that hypotheses are in the same category with facts. On page 99 the reader is given to understand that an actual hormone has been isolated from the pancreas, which has definitely known functions in connection with the carbohydrate metabolism, and absence of which explains pancreatic diabetes. On page 162 is the following more remarkable statement, "Nor must it be thought that complement and amboceptor are merely theoretical names, for each has a definite existence, and is as real as if it were a chemical enclosed in a bottle and visible to the eye." Certainly the authors' conception of reality must differ from that of the reviewer, and probably from that of their colleague in the chair of chemistry. No sentence in the book more clearly indicates its most serious defects—the confusion of explanation with fact. It is not necessary to adduce other instances. Statements either wholly inadequate or misleading are made with reference to the relation of acidosis to diabetic gangrene, about eosinophilia in whooping cough on page 148, lymphocytosis being correctly given on page 447, as to the cause of death in anaphylactic shock, and concerning paroxysmal hemoglobinuria, and pathological polycythemia. Chronic lymphatic leukemia is not mentioned in the text, though a color plate of it is copied from Cabot, nor is hemolytic family jaundice described.

The discussion of cirrhosis of the liver is excellent. It is a pleasure to find a pathologist saying frankly that he has never seen a true Hanot cirrhosis, and that this must be very rare in North America. On the other hand, the discussion of nephritis seems to the reviewer very incomplete, and to perpetuate an indefensible nomenclature in the light of present knowledge of the detailed lesions of the kidney and their mode of development. This criticism is made with full recognition of the large legitimate difference of opinion which may still exist in this field.

A final criticism applies to almost all students' textbooks in the English language. No hint is given of the historical development of our knowledge of pathology, and the book contains but one bibliographic reference. Frequent mention is made of the work of younger American and English investigators, while the great names which mark epochs in the growth of the science are nowhere mentioned. The student would never know that Virchow or Ribbert

or Cohnheim had lived, or done anything to elucidate inflammation, or thrombosis and embolism, while he was quite familiar with Fischer's theories of edema and Klotz's unconfirmed experiments on arteriosclerosis. Syphilitic mesaortitis seems to have gotten itself described without the help of Heller and Dohle, while the reader is told where to find Lewis' and Mackenzie's work on the cardiac arrhythmias—the one reference in a textbook, not of clinical medicine, but of pathology. One would suppose that pathological anatomy was as old as the Euclidean geometry, and the sources of our knowledge as obscure. One cannot be surprised that the American medical student has so little historical perspective and so little respect for thorough scholarship when one reads his textbooks. The illustrations are for the most part, unsatisfactory, a failing which must be laid at the door of American publishers rather than of their authors.

With all this criticism, the reviewer would testify to the interest with which he followed the elucidation of the many complex influences which the pathologist must reckon with today in his study of disease and its causes. The book is a readable, highly suggestive work, valuable for any student before entering on his clinical years, if supplemented by a thorough course of instruction in pathological anatomy and histology.

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THE LARGE PERSONAL FACTOR IN BLOOD PRESSURE DETERMINATIONS BY THE OSCILLATORY METHOD*

EUGENE S KILGORE
SAN FRANCISCO

I

The following letter, which explains itself, was sent to Drs R C Cabot, W B Cannon, Joseph Erlanger, A W Hewlett, Theodore C Janeway, Yandell Henderson, A D Hirschfelder, H C Moffitt and R L Wilbur

In a series of functional heart tests recently undertaken in the Students' Infirmary upon students entering the University of California a large number of determinations of blood pressure were made. Since graphic records were desired, the Erlanger blood pressure apparatus was used, and while it was writing on the smoked surface a record of the pressure oscillations in the cuff, a float in a large U-tube of mercury was writing on the same surface a continuous record of the actual amount of pressure in the cuff as it was gradually falling (Fragments of these manometric tracings will be noticed in the photographs I am sending you)

In reading the results I was puzzled in quite a large number of cases to know just what instant to choose (on the pressure oscillation records) for calculating the systolic pressure (on the mercury record). Dr R C Cabot, Dr H C Moffitt and Dr R L Wilbur were so good as to examine the records, but in the doubtful cases they did not help me to see more clearly where the systolic pressures should be read.

It therefore seemed that, in view of the number of these to us doubtful cases, and in view of the wide reputation enjoyed by the graphic oscillatory method (which undoubtedly has its best representative in Professor Erlanger's apparatus) as the most accurate for determining human blood pressures, there would be value in a comparison of the readings made independently by several different observers on the same records.

Accordingly, 100 records from eleven individuals were picked at random from a pile of about 1,300 records of 130 individuals — most all of them healthy freshmen entering college. The smoked sheets were folded together so as to expose only the oscillation records, the latter were numbered from 1 to 100, were photographed and several prints made from each plate. One set of these photographs I am mailing to you, and the others to several other clinicians and physiologists in different parts of the country. If discrepancies occur in their readings they can be expressed in millimeters of mercury by reference to the original tracings.

* From the Department of Medicine and the Students' Infirmary, University of California

Would it be asking too much for me to request your readings on these records? If you are willing to put yourself to this trouble, will you kindly

(1) Imagine yourself using the Erlanger apparatus in the ordinary way and watching the record of pressure oscillations being written as the air is gradually escaping from the cuff system and the pressure in the cuff approaches systolic pressure. Prick with a pin the oscillation written at the instant when you would read the mercury column for systolic pressure if the manometer were before you.

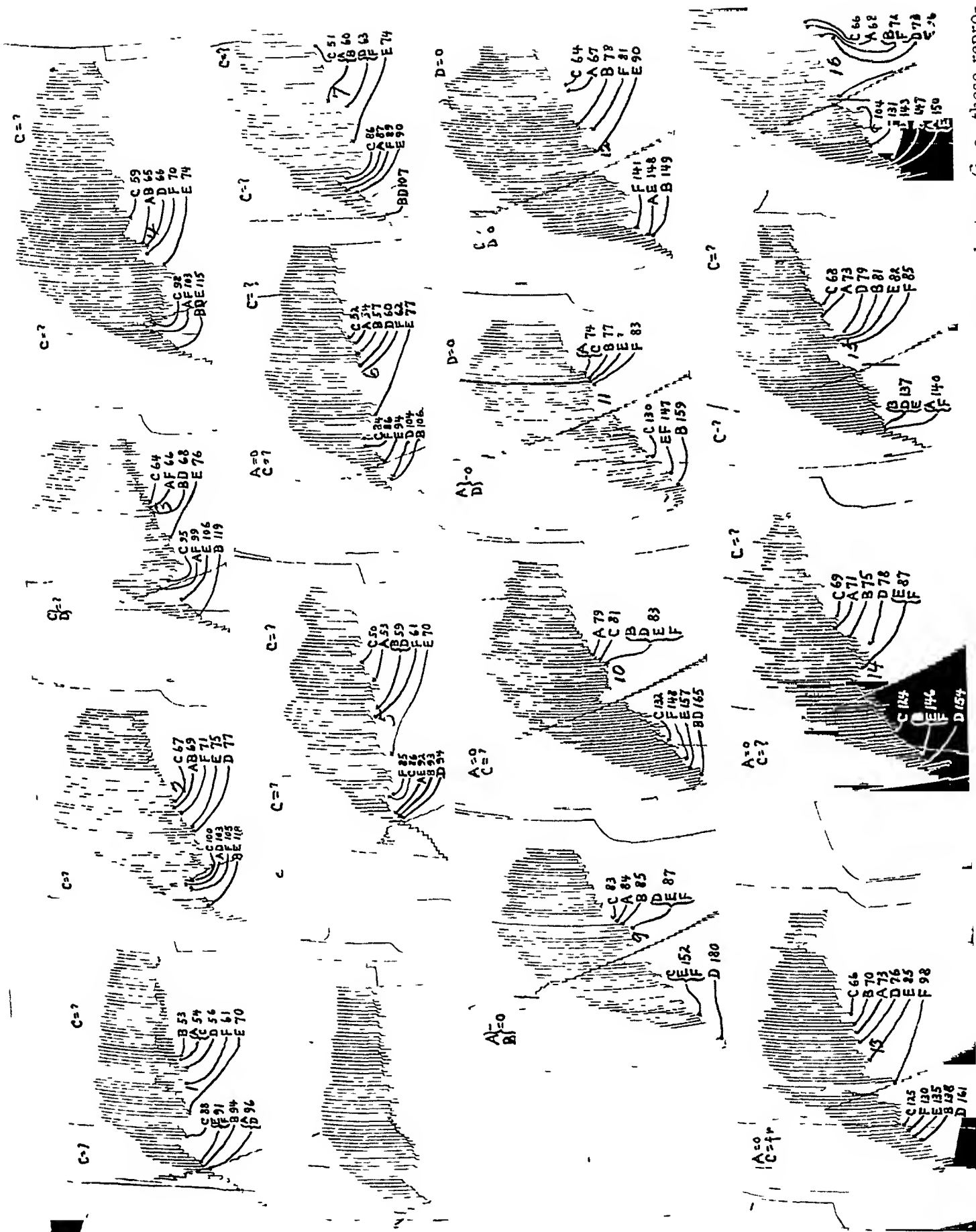
(2) Do the same for diastolic pressure. In this way mark systolic and diastolic points on each of the 100 records which you consider satisfactory ones, and if for any reason you do not give your readings on all of them, refer to them by number and give reasons for not marking them.

(3) Return the records and state what criteria you have used in marking systolic and diastolic pressures.

(4) Let me know whether you are willing (if the results should prove valuable) for your name to be published as one of a group to whom these records were submitted to be marked, without indicating which were your marks.

Drs Cannon, Erlanger, Hewlett, Hirschfelder, Moffitt and Wilbur returned the photographs with their marks, and these marks have all been transferred to the original photographic negatives which are herewith reproduced in Figures 1 to 6. Connected with each mark is a letter (arbitrarily assigned), which represents the one who chose that point for his reading, and a number, which shows in millimeters the displacement of mercury in the U-tube at the instant when this point was written. These numbers were obtained by reference to the original drum records, which contain tracings of a float in the mercury U-tube, together with its base line and, at the beginning and end of each record, stationary marks. The manometer record was measured from the midpoint of its oscillations.

It is not to be expected that every tracing taken would be suitable for reading. Rhythmic variations in the pressure, movements of the subject's arm or other accidents frequently spoil them. Such is the case with a number among this hundred, and, following the suggestion in the letter, most of those who responded made criticisms of individual tracings. Every tracing so criticized is marked "f r" (faulty record) following the letter which indicates the observer who made the criticism. This abbreviation is placed in the upper left hand corner if the criticism refers to the part of the record from which systolic pressure is to be determined, and in the upper right hand corner if it refers to the "diastolic part" of the tracing. In the same way, a question mark is used to indicate that doubt was expressed about the reading without criticizing the tracing, and a zero means that no mark was made. In some cases the question was inferred from the presence of two marks for systolic or diastolic readings. Failure to mark individual records in some cases seems intentional on account of doubt about where to put the marks, in other cases it seems to have been due to oversight.



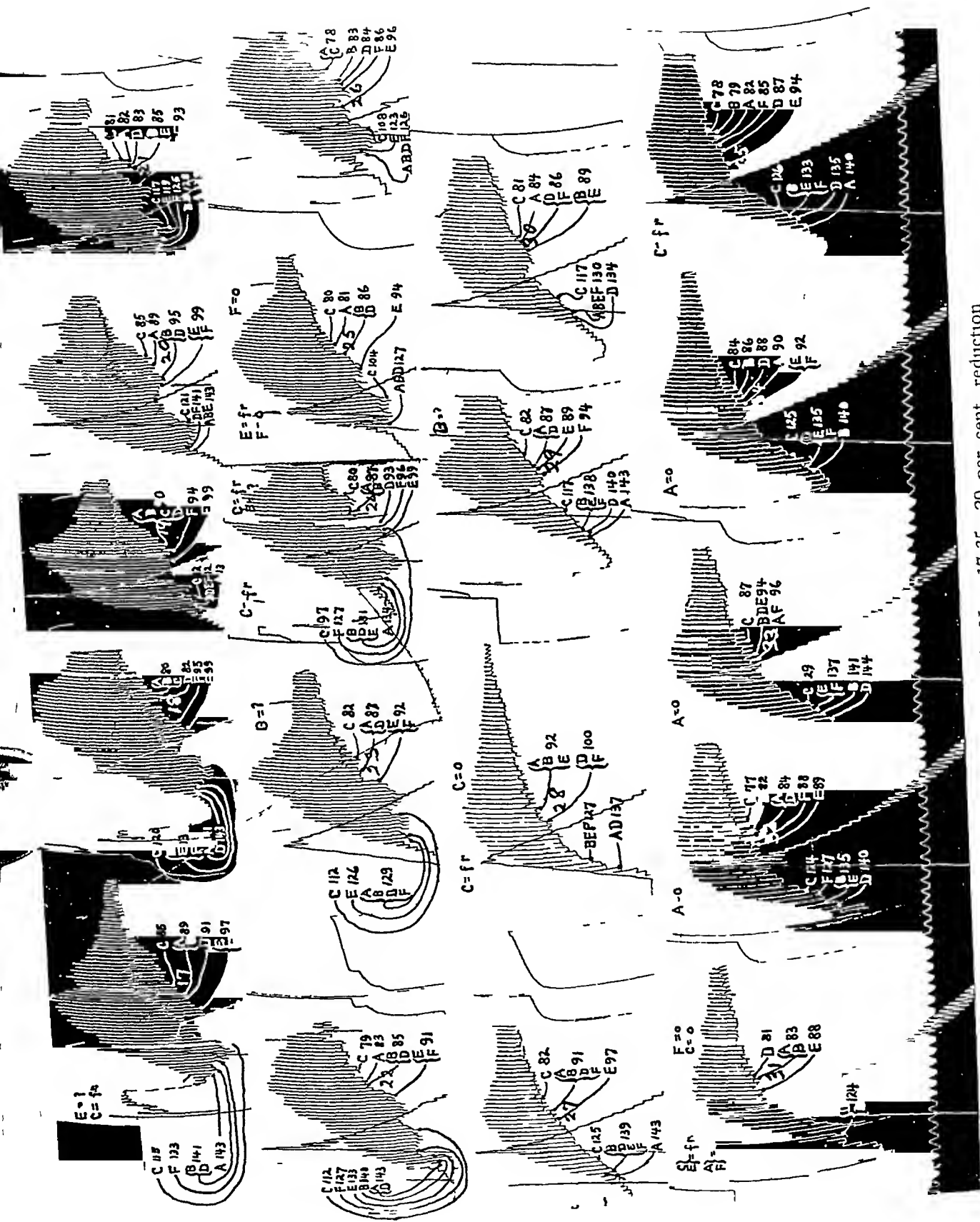
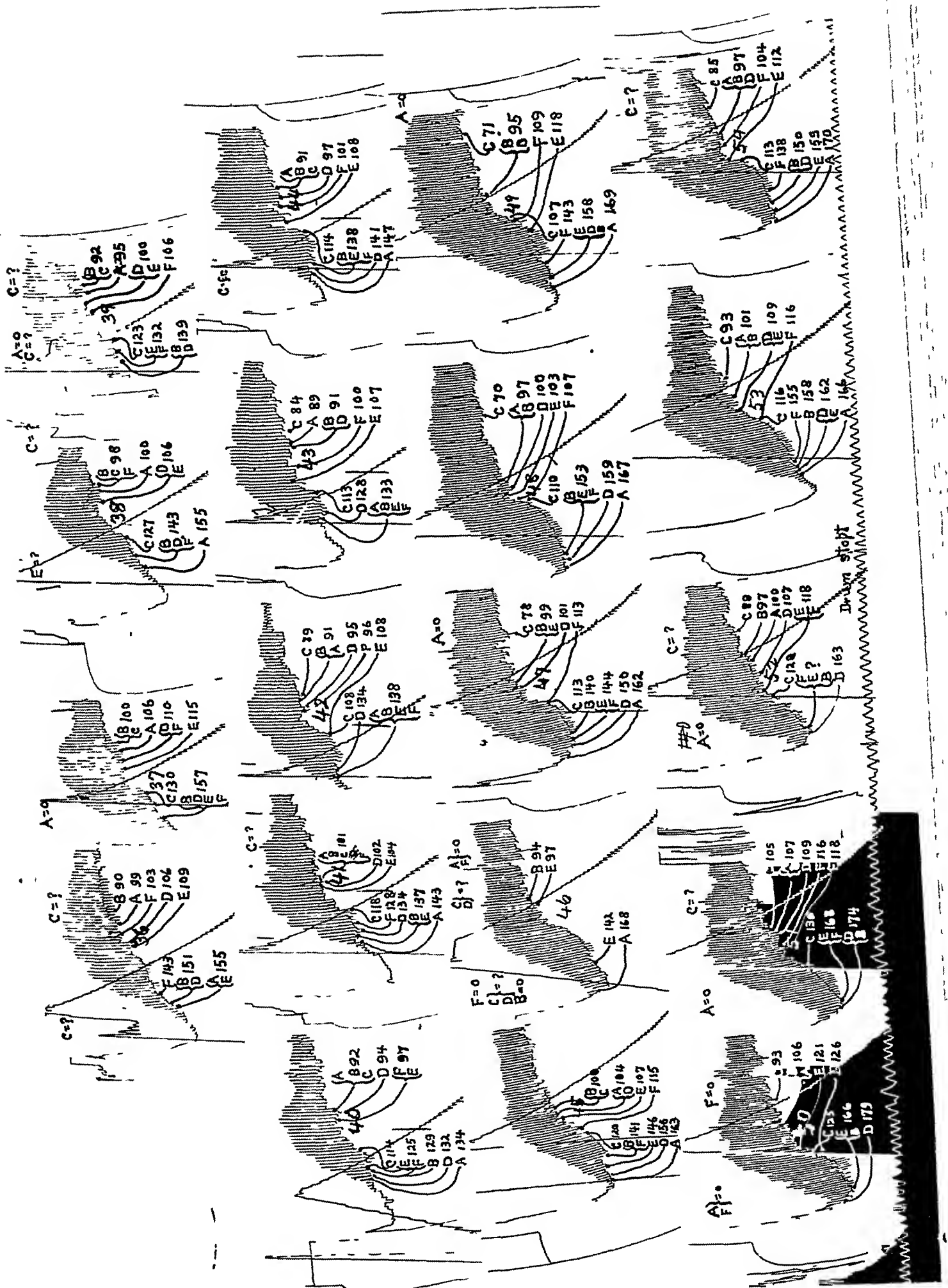


Fig 2—Same as Figure 1, Nos 17-35, 29 per cent reduction



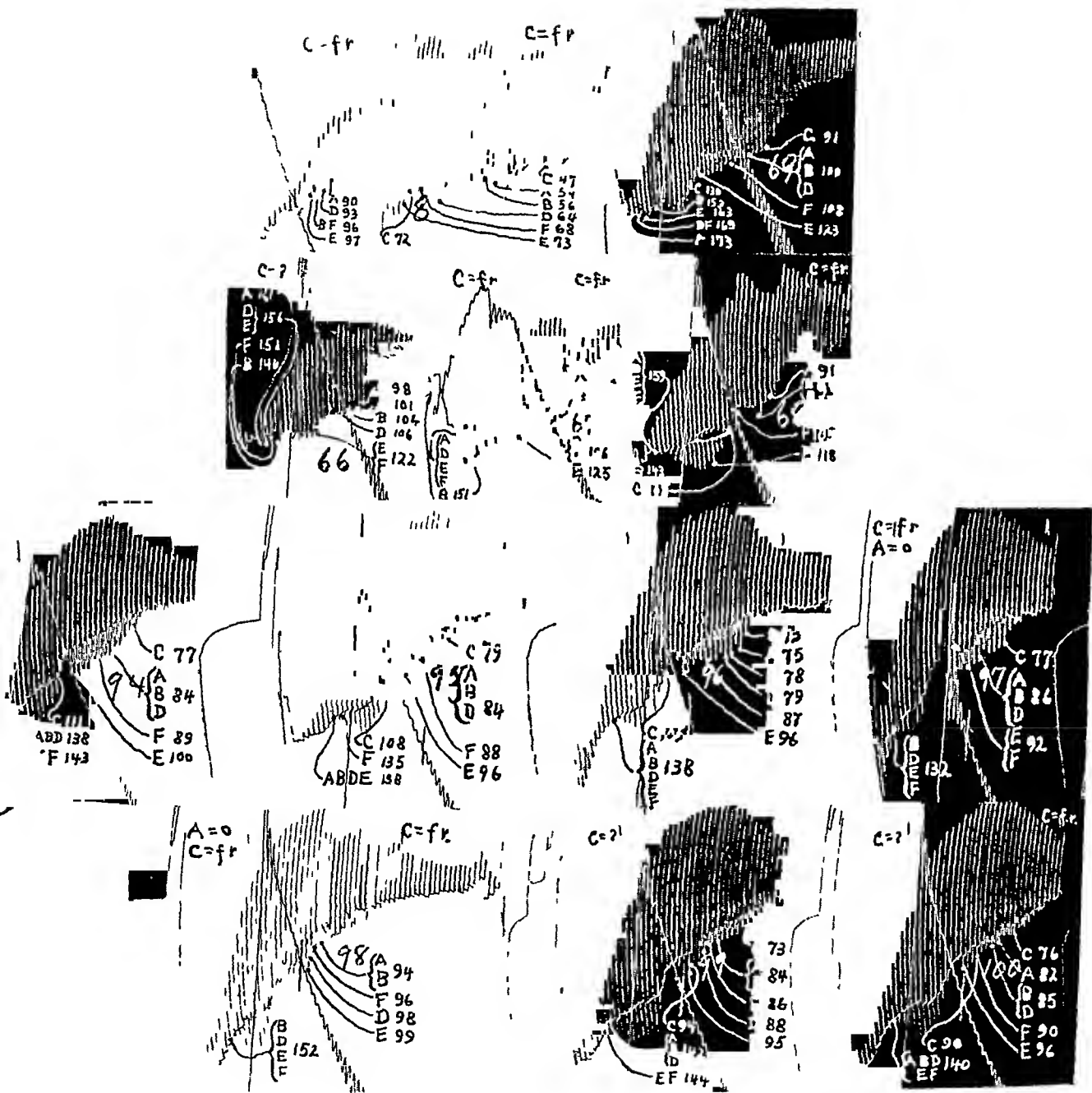
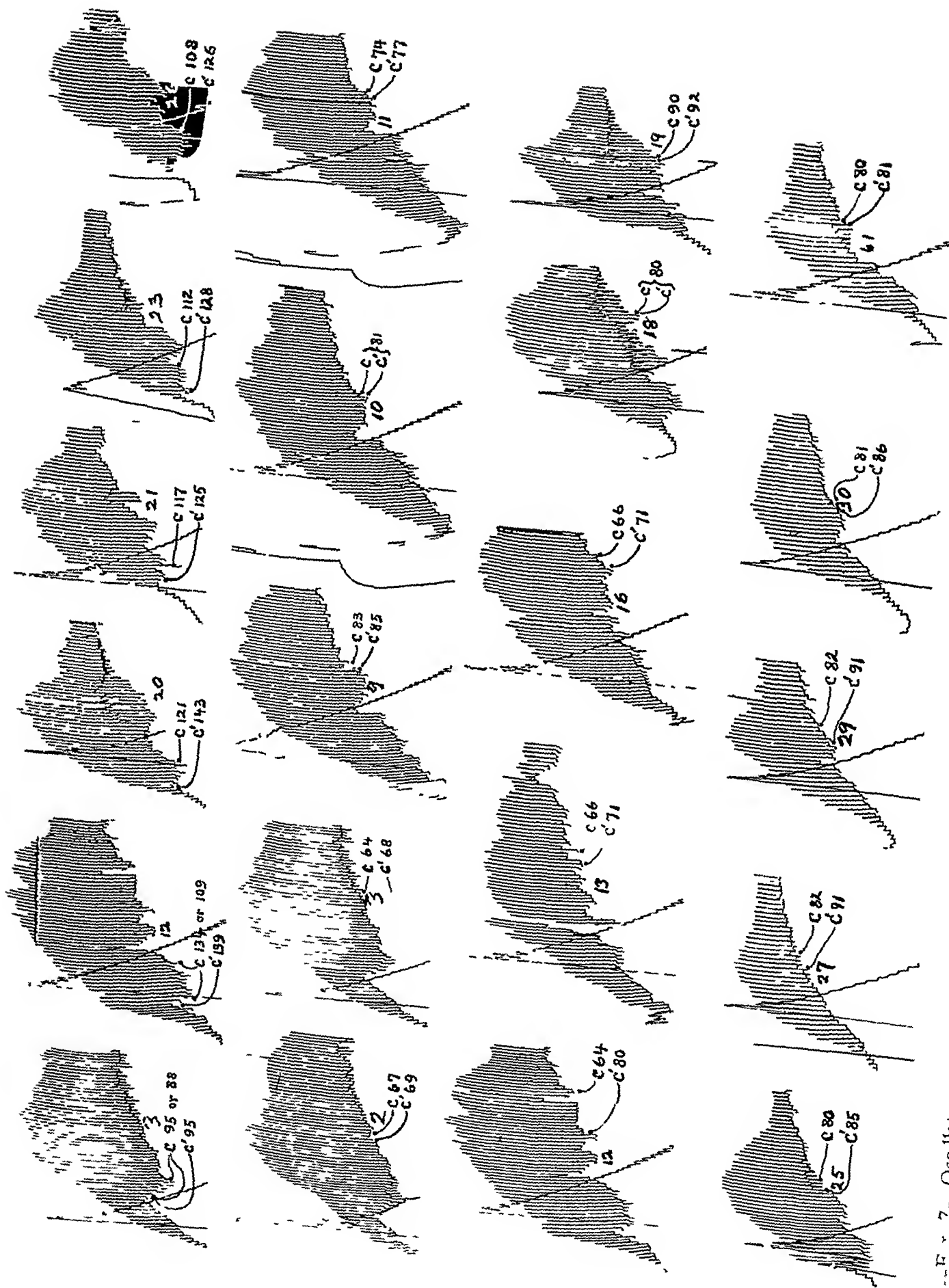


Fig 6—Same as Figure 1, Nos 8, 66-69, 94-100, 17 per cent reduction



In glancing over the illustrations it will be noticed that there is comparatively little agreement with regard to which records are suitable and which are not. "C," for example, who criticizes or questions many tracings which all the others consider satisfactory, marks without hesitation a number of records which are not clear to them

As a basis for comparing the readings by different men, only those records are taken which were marked by all six and were not classified as faulty or doubtful by any of them. If only one observer failed to mark a record (although in some cases this appears to have been due to oversight), or made two marks for systolic or diastolic reading, or expressed doubt about his mark, that record was thrown out. Or, strictly speaking, that part of the record ("systolic part" or "diastolic part") was thrown out. So that, in the tabulation which follows, it is to be understood that the only tracings referred to are those which met with unanimous approval,¹ and they are to be recognized in the illustrations by the absence of notations above them. There are thirty-six such tracings for comparison of systolic determinations and fifty-six for diastolic

THE SYSTOLIC READINGS

In almost all cases there is a great dispersion of points chosen for systolic readings. In tracing No 19, concerning which there is least disagreement, there is a difference of 8 mm of mercury between the highest and lowest mark, while in No 49 the difference is 62 mm. of mercury.¹ Figure 9 shows the relation between the number of records and the amount of this scattering. It will be seen that a majority of the tracings show differences between highest and lowest marks of from 15 to 35 mm of mercury. The average is 29 mm or 22.2 per cent of the average of all the systolic readings.

The surprising magnitude of these discrepancies prompts an inquiry concerning the possible causes.

That many of them are due to the lack of uniformity of ideas with regard to the criteria is suggested by the fact that the readings of certain observers are usually higher than those of others. Thus, the average of "C's" thirty-six systolic readings is 110 mm of mercury, while that of "F" is 132.5, of "B" 133.4, of "E" 134.5, of "D" 135.7, and of "A" 138.4. The statements of their criteria are the following

"A" A sudden increase in the amplitude of the beats, especially when this involves a fall beneath the base line

"B" I either used the moment of sudden increase in the height of the curve, or when this wasn't clear, a little jump in the curve which Erlanger has described as a criterion

1. One general criticism referring to the speed of the drum will be referred to later.

"C" The sudden increase in amplitude of oscillations, and especially change in form of oscillations

"D" The point at which the upper and lower margins of the oscillations diverge to form a \sim In doubtful cases this is often aided by the presence of a small shoulder to the right of the descending limb

"E" Two guides, sometimes one, sometimes the presence of both, were used as indicators for the systolic blood pressure, that is, (a) the first decided increase in the excursions of the lever and (b) the presence of the small shoulder at the base of the line recording the fall of the lever

"F" Did not state his criteria

Thus it appears that "A," "B" and "D" look primarily for the sudden increase in amplitude, the two latter resorting to the change in form of the wave in doubtful cases, "E" uses either of these criteria without preference, while "C" looks especially for the change in form. The significance of these variations in the understanding of the criteria will be referred to later



Fig 9—Relation between the number of tracings and the scatterings of the systolic marks. Numbers at left represent percentages of total number of tracings (36) accepted for the analysis, at bottom the differences between highest and lowest readings on a tracing expressed in millimeters of mercury

THE DIASTOLIC READINGS

The scattering of points marked for diastolic readings is about as extensive as for the systolic readings. In Tracings 9 and 10, concerning which the disagreement is least, the difference between highest and lowest, expressed in millimeters of mercury, is 4 mm. The greatest difference is 46 mm in No 91. Figure 10 shows the relation between the number of records and the amount of scattering. Here the greatest number of tracings shows a scattering of between 10 and 25 mm of mercury. The average is 18.5 mm. While, absolutely, this figure is less than the average scattering of systolic readings, it is relatively practically the same, that is, 21.3 per cent of the average of all the diastolic readings.

Here again, certain observers usually make the low marks, and others the high ones. And again the discrepancies may be explained by differences in the ideas as to the exact criterion of diastolic pressure. The following quotations indicate the criteria of "A," "B," "C," "D," and "E"

"A" The criterion for the diastolic pressure was the last of the large beats, that is, the beginning of the definite diminution in size

"B" The diastolic pressure was placed according to the rule that it coincides with the last oscillation of maximum extent

"C" The first sudden and consistent diminution in amplitude of oscillations

"D" The diastolic pressure was estimated by the last of the beats of maximal amplitude

"E" I have chosen the first apparent maximum oscillation without making measurements of the tracings

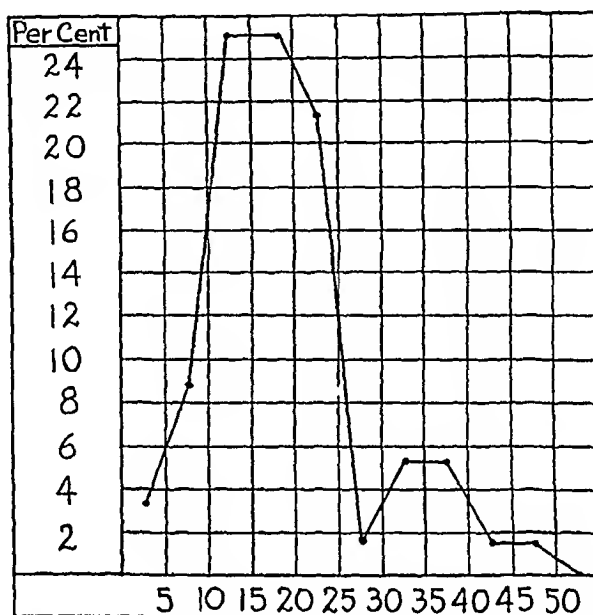


Fig 10—Relation between the number of tracings and the scatterings of the diastolic marks. Numbers at left represent percentages of the total number of tracings (56) accepted for the analysis, at bottom the differences between highest and lowest readings on a tracing expressed in millimeters of mercury

The ideal tracing on which these five might agree would show oscillations steadily increasing to a maximum and then at once diminishing abruptly. But if this condition fails to occur, the opportunity for confusion arises. In tracings like Nos 1, 3, 35 and 52, in which a number of the largest oscillations seem to have about the same amplitude "E" will mark the first of them, "B" and "D" the last of them. If, following these maximal oscillations, the reduction in size is not at once abrupt, as it very often can hardly be said to be, "A" will wait for a "definite" and "C" for a "sudden and consistent" diminution in amplitude.

"B" and "D" define their criterion in almost exactly the same words, and yet in only seventeen out of the fifty-six records do they

prick the same spot. Their differences vary up to 36 mm of mercury (No 90) and average 4.5 mm, even though their criterion would seem to be the easiest to follow. Of course, they used only the eye for measuring the length of strokes, but they had the advantage of leisure, of having the completed tracings before them, and of confining their attention to the oscillation record exclusively, which is not the case in the ordinary use of the Erlanger apparatus, using the method of continuous escapement.

"A" and "C" seem to express practically the same idea with regard to the diastolic criterion, namely, the first more or less abrupt contraction in the length of the strokes after passing the maximum. But intervals between their marks are more constantly found and have a higher average than in the case of "B" and "D." They have to gauge not only the length of the strokes to determine the maximum, but also the rate of decrease in amplitude from point to point in the tracing, and they have to decide where this decrease becomes "definite," or "sudden and consistent." One does not have to look far to see the difficulties involved in these judgments, for example Nos 23, 79, 82, 83.

THE PULSE PRESSURE

The pulse pressure, being the difference between systolic and diastolic pressures, shows in these tracings a combination of the vagaries from the two sources. Twenty-eight of the tracings escaped specific criticism for both systolic and diastolic determinations. Among these it is possible to compute from identical tracings pulse pressures all the way from 3 to 97 mm of mercury (No 48), from 0 to 73 (No 53), etc. The average of the lowest computable pulse pressures in these twenty-eight records is 13 mm, of the highest, 58 mm. And in several of the records which were thrown out on account of a single criticism, relating to the speed of the drum, the lowest computable pulse pressures are minus quantities—in No 90—27 mm of mercury, that is, one observer's diastolic reading is actually 27 mm higher than another's systolic reading. Of course, such results could not occur if the computations were limited to the marks of any one individual.

II

As has been stated, there was among those who marked the tracings some lack of uniformity of ideas as to exactly what phenomena constitute the oscillatory criteria both for systolic and for diastolic readings. It seemed very desirable, therefore, to determine how much variation may occur in the choice of reading points when the possible occurrence of this disturbing factor (difference of ideas with regard to the criteria) is removed. This would be shown by a comparison

of two sets of marks made at different times by the same individual on copies of the same tracings, the second marking to be done after a considerable time interval. Dr Erlanger has very generously consented to be the subject of this experiment, and has marked systolic and diastolic points on a fresh set of photographic prints identical with the ones which he with the others had marked before. The first prints were marked in December, 1912, the second in November, 1913. Both times he responded to the request to indicate which tracings were to be considered unsatisfactory for reading, referring to the tracings by number and making remarks favorable or otherwise about most of them, in 1913 he did this without referring to the copy of his 1912 letter. Both times he made the general criticism that the slowness of the drum interferes with the recognition of the change in form of the down strokes. For systolic readings there were classified specifically as faulty or doubtful forty-four tracings in 1912 and ninety-two in 1913, for diastolic readings thirty-two in 1912 and sixty-one in 1913.² Some tracings, such as Nos 9, 10, 32 and 33, which were given systolic marks without comment in 1912, are described in 1913 as "not legible." Nos 94 and 95 each have two widely separated marks in 1913 and one mark without comment in 1912, No 41 in 1912 was said to be doubtful for diastolic reading, in 1913 the diastolic mark is placed without question, both marks, however, very near together.

As a basis for comparing readings made at the two times only those tracings have been used which escaped specific criticism both years. Of these there are six for systolic readings (Nos 3, 12, 20, 21, 23 and 26, the top row in Figure 7) and thirty-two for diastolic readings (the remainder of Figure 7 and Figure 8). On these plates C indicates the first marking and C' indicates marks placed eleven months later. The values in millimeters of mercury are given; they have been determined as described in Part I.

SYSTOLIC READINGS

In each of Records 3 and 12, two points for systolic reading were marked in 1912. These have been included because it was specifically stated in 1913 that No 3 "seems satisfactory"; although in other instances the marking of two points on a tracing for systolic or diastolic reading has been considered reason for excluding that tracing. In No 3 the 1913 mark is the same as one of the 1912 marks, and in No 12 it is within 5 mm of mercury of one of the 1912 marks. In the remaining four systolic comparisons the differences between the 1912

² Whenever the criticism of a tracing was not clearly stated to refer either to the systolic or diastolic part of the record it was assumed to refer to both parts.

and 1913 marks are respectively 22, 8, 16 and 18 mm of mercury, an average difference of 16 mm or 13 per cent of the average of these eight readings. Among other tracings which escaped specific criticism either in 1912 or 1913, but not both times, there are still larger discrepancies between the two systolic marks, which run as high as 30 mm of mercury in Tracing 8.

DIASTOLIC READINGS

Among the thirty-two diastolic comparisons the differences range from 0 to 16 mm of mercury, and average 5.4 or 6.9 per cent of the average of these readings. Among some of the other tracings which escaped specific criticism in one of the years there are differences in diastolic readings up to 23 mm of mercury in Tracing 47.

DISCUSSION

The principal object which has led to the use of the oscillatory criteria instead of simple palpation or auscultation of the artery below the cuff is the avoidance of errors involved in the identification of the criteria—tactile sensation and even hearing being supposedly less sensitive for this purpose than vision. Only an occasional statement in the literature of the subject is at all skeptical,³ and the feeling is general that the clinical use of the simpler methods of palpation and auscultation is dictated by economy and convenience at the expense of a certain amount of accuracy. Of course, this preference should not be given to vision without a consideration of what the observer is expected to see, and it is remarkable that the oscillatory criteria have received such general acceptance on this basis without any attempt being made heretofore to determine the personal factor involved in their identification and to compare it with similar sources of error in the use of other methods. Tests comparable as closely as possible to those here reported have now been applied to the palpatory⁴ and auscultatory⁵ indices, and the analysis of the results is decidedly favorable to the simpler methods.

This investigation has nothing to do with the general question of sources of error in blood pressure measurements, which has been reviewed elsewhere.⁵ It has no bearing even on the truthfulness of the oscillatory indices, once they are accurately identified, and it is in no wise to be regarded as an attack on the important experimental work of Erlanger and others in support of the validity of particular oscillatory criteria. It is concerned solely with the quantitative deter-

³ Cordier and Rebattu. *Arch. d. mal. du coeur*, 1911, iv, 737.

⁴ Kilgore, E. S. *California State Med. Jour.*, March, 1914.

⁵ Kilgore, E. S. Page 927, this issue.

mination of the personal factor which operates in the clinical interpretation of these criteria, and it shows that this factor may be surprisingly great. The six men who made the experiment possible by submitting their marks fortunately are physiologists and clinicians whose qualifications cannot be questioned.

The first important fact to appear is that there is little agreement with regard to the fitness of individual oscillatory records, which to accept for reading and which to throw out. The records were not selected in order to show difficulties but were taken at random from among hundreds of others, and with the exception of one statement with regard to the speed of the drum, which will be referred to later, no one has made any general criticism of them.

The second exhibit is the variety of understandings as to the exact criteria both for systolic and for diastolic pressure. This alone is sufficient to invalidate all reports of blood pressures obtained by the oscillatory method which do not state very precisely the criteria employed. The claims of these various criteria cannot be discussed here, but, in view of the extensive use of this method in the past, not only in practical clinical work but also by investigators as a "control" or means of standardizing other methods, it is important to emphasize the fact that *there is not a general and exactly uniform understanding of the criteria*⁶.

It is evident from a comparison of the systolic marks made by different observers and their statements of the systolic criteria that some of the confusion here arises from the attempt by different men to follow two different criteria, which often appear not to coincide.

The sudden increase in amplitude ("principle of von Recklinghausen") is the criterion generally accepted among those who employ the oscillatory method with whatever instrument used. Erlanger,⁷ after extensive experiments, adopted it for use with his graphic method, and later⁸ described the "change in form" of oscillation record (a shoulder on the down stroke) as an additional systolic criterion. Both have been given adequate theoretic and experimental support, and they should of course and in selected instances do

⁶ Nearly always among the diastolic marks "E" is highest and "C" lowest. The differences between these two are responsible for a considerable part of the total average discrepancy, and the omission of either "C's" or "E's" marks reduces the average by 5 mm of mercury. It is not the purpose of this paper to offer criticisms or suggestions about the marks, but it is fair to point out that in all probability a considerable part of the diastolic differences of "C" and "E" could have been avoided by a previous conference between them. Their statements of the criterion, it will be recalled, were not the same.

⁷ Erlanger, Joseph. Rep. Johns Hopkins Hosp., 1904, xii, 53.

⁸ Erlanger, Joseph. Am. Jour. Physiol., 1908, xxi, 24.

obviously occur at the same points in the tracings, but it is also a fact that in practical application on human beings they frequently lack at least the *appearance* of doing so

When these tracings were made it was not considered desirable to make a special comparison between the two systolic criteria, and a rather slowly moving drum was used, thus bringing the strokes moderately near together and accentuating changes in amplitude, on which depend one of the systolic criteria and the only available diastolic criteria. This compacting of the records has rendered the change in form less conspicuous and in some instances has obscured it entirely. One general criticism (to be referred to again) has been made on this account, hence, even though the change in form is distinct in many of these curves they are not to be urged as examples of the apparent failure of the two criteria to coincide. But reproductions of oscillatory curves appearing in the literature show the same characteristic—for example, a tracing published recently by Erlanger and Festerling.⁹ By actual measurements the approximate lengths in millimeters of successive up-strokes (here designated consecutively by letters) from the beginning of the first oscillations are (a) 0.3, (b) 0.6, (c) 0.4, (d) 0.4, (e) 0.5, (f) 1, (g) 2, (h) 2.4, (i) 4.4, (j) 6.3, (k) 6, (l) 7.8, (m) 7, (n) 6, (o) 7.9, (p) 7.3, (q) 6.9.

The change in form begins definitely with Stroke m. At this point the increase in amplitude, as the measurements show, is a minus one as compared with the abrupt positive increases in the region of Strokes e to i. The greatest single absolute increment is between Strokes i and j, the greatest relative increments between Strokes e and f and between f and g.

Certainly both of these criteria should not continue to be relied on unless at least an understanding of them can be reached which will prevent their ever appearing to conflict, and in these experiments it may be presumed that if the observers had all confined themselves to one criterion and marked only the records in which this was clear, the differences in systolic readings might have been less. But—

Third. The very great discrepancies disclosed between the readings of different observers are only partly explainable by variations in the understanding of the criteria. Those who endeavor to follow what appear to be identical criteria frequently choose widely separated reading points both for systolic and for diastolic readings.

Fourth. After completely eliminating the possibility of variations in the understanding of the criteria influencing the results, there still remain large disagreements in the choice of reading points. The one who may be presumed to be best qualified in this country to identify the

⁹ Erlanger and Festerling. Jour. Exper. Med., 1912, xv, 370, Figure 4b.

oscillatory criteria, seldom on second trial duplicates his first marks, and often misses them by a wide margin. His average discrepancy for thirty-two diastolic comparisons is 5.4 mm of mercury or 6.9 per cent, of the average of all these diastolic readings, the average discrepancy for the four systolic comparisons is 16 mm of mercury or 13 per cent of the average of these systolic readings. In connection with this systolic result must be taken into consideration the general criticism mentioned above, and to be referred to again, relating to the slowness of the drum.

Fifth. In weighing the results of these experiments as a whole it must be remembered that several sources of error have here been excluded which are present in actual practice with the Erlanger apparatus. In using the ordinary method of continuous escapement it is necessary to divide the attention between the smoked record and the mercury column, to decide about the criteria the instant they are supposed to occur without having the completed tracing for comparison, and to read the level of the mercury column at once, the latter itself being in active up and down movements. In this experiment the observers have had the benefit of unlimited time for consideration, of reading records already completed, and of giving them exclusive attention. The conclusion is inevitable that in actual practice by these observers, if they worked independently and *relied exclusively upon the oscillatory criteria*, using the ordinary method of continuous escapement, their blood pressure measurements would be even more discordant than is shown here.

Sixth. Whatever this experiment shows with regard to the personal factor in the results obtained by the Erlanger instrument would seem to apply with even greater force to the use of all the other blood pressure instruments hitherto described, with which the oscillatory criteria exclusively are used, for with the possible exception of a photo-registration method, Erlanger's instrument appears to be unquestionably the most perfect on the market for the purpose for which it is designed, namely, to show graphically the pressure oscillations in the pneumatic cuff used for compression. Uskov's apparatus¹⁰ has no features to save it from the discordant readings exhibited in this experiment, but on the contrary, it has been clearly shown¹¹ to have unequal sensitivity at different pressures—a condition calculated to distort markedly the oscillatory criteria. Another well-known graphic instrument is that of Gibson,¹² which registers the oscillations of the

10 Uskov. Ztschr f klin Med, 1908, lxxvi, 90

11 Erlanger, Joseph. A Criticism of the Uskov Sphygmotonomograph, THE ARCHIVES INT MED, 1912, ix, 22

12 Gibson. Quart Jour Med, 1907-1908, i, 103

mercury column itself. The change in form of the wave does not appear at all in these tracings, and the changes in amplitude are gradual. Simultaneous records made by an Erlanger oscillation recorder and a float in a mercury manometer, both connected with the same cuff, show very gradual alterations in amplitude of the swings of the mercury column even when the amplitude changes in the other record are quite pronounced. Mercury is far too heavy to respond promptly to these changes in oscillation amplitude.

Many blood pressure instruments are supplied with a pointer on a dial, a pith ball or drop of fluid in a glass tube or other device for exhibiting pressure oscillations in the compressing cuff without making a graphic record. The observer is expected to carry in his mind the amplitude of preceding oscillations and accordingly to form his judgments of the amplitude changes. It is evident that in this attempt he is still further handicapped by not having before him a graphic record of the oscillations preceding the place where he makes his reading.

Professor Erlanger, who does not entirely agree with the inferences which it seems to me must be drawn from these experiments, is kindly stating his views in an accompanying paper. The points in his article which it would seem advisable to mention in this separate connection are the following:

1. The Conditions Affecting these Experiments. In so far as the recognition of the "change in form" is concerned, Professor Erlanger is justified, I believe, in his two general criticisms relating to the adjustment of the apparatus, namely, that the smoked surface traveled more slowly and that the writing lever magnification was greater than optimum, or rather that the relation between these two adjustments was not the best for showing the "change in form." So that, although the "change in form" is quite clear in many of the tracings, and although all tracings were omitted which seemed doubtful to any of the observers, yet it is fair to reserve judgment of the personal factor involved in the use of that criterion. In common with the majority who, up to the present time, have attempted to use the oscillatory criteria with whatever instrument, I was looking especially for the sudden increase in amplitude as systolic index. As has already been explained, this as well as the diastolic criteria, is rendered more distinct by the slower drum, and the same is true of the greater lever magnification.

That Professor Erlanger has now abandoned "the first sudden increase in amplitude" as an index of systolic pressure in the method of continuous escapement is an important announcement, which especially deserves consideration by those who are still advocating the use

of the oscillatory criteria with nongraphic instruments So far as I am aware, no one claims, without the employment of graphic oscillatory records, to be able to use either the "change in form" as a criterion or the oscillatory indices by the method of intermittent escapement.⁷ Additional sources of error in interpreting oscillatory indices with nongraphic instruments have already been pointed out

With regard to all the oscillatory criteria except the "change in form," I do feel that, for the purposes of this investigation, the conditions under which the curves were obtained and interpreted were excellent While the presence of the graphic manometer record obviated the necessity of immediately reading the mercury level, efforts were not lacking constantly to adjust the apparatus to get the best curves, and the resulting mixture of good and bad tracings is what always occurs in practice The personal factor immediately becomes evident in selecting the tracings which should be read, and one of the important showings of these experiments is the magnitude of the personal factor which enters into this choice No practice of "redetermining the end-points" in doubtful curves could obviate the necessity of first deciding which were the doubtful tracings Most of those who marked the records gave free expression to doubts or criticisms connected with individual tracings, and, while these criticisms did not agree, all the tracings were thrown out of further consideration which received an expression of doubt from any one of the six men—a weeding-out process considerably more radical than would be the case if one of these men were using the method in practice It certainly does not seem too much to assume that the tracings which remain after this more than ordinary discrimination represent at the most the ones which the average person using the method would attempt to read without further checking up the "end-points" by other methods And if these selected tracings are not to be relied on without verification from outside sources, it is difficult to see what circumstances would ever enable them independently to be given full confidence

2 The Factor of Interest or Concern It is true that these six observers were busy men They were at liberty to decline to spend time with this matter, but, having once consented to be subjects of a scientific experiment, it is entirely fair to assume that they did not slight it, but that, on the contrary, if there was any difference between their psychologic attitude to this task and to the ordinary one of routine blood pressure determinations, their more careful efforts were bestowed here And, however gloomy may be the outlook for quantitative clinical methods in view of "E's" failure to mark the maximum oscillations, it is impossible to derive reassurance from the assumption that he would have done better if his judgments had been

formed in haste on uncompleted records and with his attention divided between them and the mercury column

3 The Factor of Judgment The quantitative determination of the effect of this factor, it must be remembered, has been the chief object of this investigation Professor Erlanger believes that the absence of a series of determinations obtained from each subject "at the same sitting and under as nearly the same conditions as possible" has deprived the observers of a "legitimate aid to the formation of a judgment" My answer is that the usual shifting character of blood pressure due to respiration or other causes makes series of determinations always preferable to single ones in actual blood pressure measurements with any method, but that within the scope of this investigation, which is sharply limited and which does not include actual blood pressure measurements, such series would be out of place To illustrate, if the problem put to these observers had been to determine the blood pressure of a given subject, it would have been advisable for them to rely on a series of readings from this subject, and they would have been confronted with the double task of first making the individual readings in the series, and, second, if there was variation in the results, deciding what values to accept In this experiment, on the contrary they have had but the one problem of selecting the reading points in the individual tracings, and all that was necessary in order for them to obtain 100 per cent accuracy within the limits of this investigation was to throw out the ambiguous records and choose identical reading points in the remainder, even though the corresponding reading of the manometer was far from the true blood pressure The requirement of a series of graphic records, in order to discredit individual tracings which by themselves apparently are legible, is certainly a testimony to the uncertainty of the criteria afforded by those tracings

Moreover, in order to utilize a series of records from the same subject to check up individual readings in the series, it is necessary as Professor Erlanger suggests, to assume that all were taken under practically the same conditions, that is, at practically the same blood pressure Yet in another place he refers to the well-known fact that the blood pressure cannot be depended on for stability, but frequently undergoes considerable variations over periods of a few moments To the credit of the palpatory and auscultatory indices it should be remembered that readings by these methods suffer no indefiniteness on account of changes in blood pressure

4. The Comparison of the Diastolic Marks Made by One Observer In connection with the average discrepancy of 5.4 mm of mercury or 6.9 per cent, the following facts must be taken into consideration

(a) This 69 per cent is not a measure of the total error involved in the method, but only of that due to one factor, namely, the judgment latitude of a single observer in selecting the reading points. It must be presumed that this latitude would be increased if the judgments of more persons were involved, however uniform their training in regard to the criteria to be looked for. In practice, also, the personal factor plays a further rôle in reading the manometer, and as in other methods, additional sources of error, such as resistance by artery walls or arm tissues, may assert themselves. Furthermore, if my contention is correct that single tracings rather than a series from the same subject offer the proper basis for determining the play of judgment in identifying the criteria, then the chances for minimizing the personal factor in this effort were considerably better in this experiment than in actual practice, because of the opportunities here enjoyed of marking completed tracings without the need for hurry in making the decisions or for diverting the attention from the tracings to the manometer.

(b) Notwithstanding the elimination of doubtful tracings both times they were marked, discrepancies as high as 16 mm of mercury occur, and among records which were accepted one year but not both years discrepancies as high as 23 mm of mercury are found.

(c) Parallel experiments with the auscultatory diastolic criteria⁵ although necessarily containing additional sources of error, connected with the reading of the manometer and the inclusion of the readings of two observers instead of one, have shown discrepancies averaging only one-third to one-half as much as in this test.

The limitation of the scope of this investigation must again be emphasized. No evidence is presented either for or against the correctness of the oscillatory indices *once they are accurately identified*. The fact that individuals who express the criteria in almost the same words may really understand them quite differently is important, and will give special interest to the rediscussion of the identifying features of the curves in Professor Erlanger's article. These experiments should by no means be counted to the discredit of graphic methods in general, but they will do good if they are accepted as strongly emphasizing the need for more careful discrimination in the use of instrumental clinical procedures which lay claim to special accuracy.

I am very grateful to Drs Cabot, Cannon, Erlanger, Hewlett, Henderson, Hirschfelder, Janeway, Moffitt, and Wilbur for their cooperation. It will of course be understood that those who submitted themselves as subjects of these experiments are in no way thereby committed to the method. Drs Cabot, Henderson, and Janeway, who did not mark the tracings, permit the publication of the following extracts from their letters which show why they did not.

R. C. CABOT. I must confess myself totally unable to mark any point to be regarded as the diastolic pressure in the tracings which you sent me. I am very glad you are bringing out the unreadability of Erlanger's records.

YANDELL HENDERSON After looking over your records, it is quite clear that in the majority there is *no one* maximal pulsation that would mark diastolic pressure. They confirm my previous opinion that even the Erlanger instrument usually gives a very indistinct criterion of diastolic pressure. The point of sudden increase at systolic pressure is clearer, although often also obscure. My answer is then that there are *no sharp* points of transition, and it would be useless to mark what is *not there*. It would be mere guess work.

THEODORE C. JANEWAY I found long ago that in many cases it was quite impossible to determine the lowest point of maximal oscillation on an Erlanger record, or in any other way. In some pulses the point is fairly clear cut, but I believe they are in the minority. Since the introduction of the auscultatory method, I have lost my interest in the oscillatory and have given the matter no thought. So far as estimation of the systolic pressure is concerned, I do not believe in attempting this by any device which registers changes in the position of artery being compressed, and I have at no time used the Erlanger systolic index. Auscultation checked by palpation immediately below the cuff makes, I think, the best method for systolic readings.

AN ANALYSIS OF DR KILGORE'S PAPER "THE LARGE PERSONAL FACTOR IN BLOOD PRESSURE DETERMINATIONS BY THE OSCILLATORY METHOD"

JOSEPH ERLANGER, M D
ST LOUIS

In a spirit that cannot be too highly commended, Dr E S Kilgore has submitted to me the first draft of his manuscript together with a letter stating that "it would be decidedly to the advantage of the truth-seeking medical public if, after reading my manuscript, you would present your criticism in the form of an article to appear in the same journal number. If you will do this I should like to have the privilege of reading your manuscript and, if indicated, altering my own, and we would then exchange manuscripts again until there were no further changes to make"

Convinced by my experience as well as that of others, with the graphic oscillatory method of determining the blood pressure, by the satisfactory check to which it has been subjected by the experiments on animals, performed by myself and others, and by observations made both by myself and others, in which, at the same time, the blood pressures have been determined by the palpatory, oscillatory, auscultatory and subjective methods, that the oscillatory criteria, when properly checked, are not alone as sharp but are also as accurate in the determination of the blood pressures as any other known method¹ while possessing the additional advantage of objectiveness, I feel that lest the effect of Dr Kilgore's critical studies may be to

* Submitted for publication July 2, 1915

* From the Physiological Laboratory of Washington University, St Louis

¹ Since this was written I have had the opportunity of reading Dr Kilgore's manuscript on "A Quantitative Determination of the Personal Factor in Blood Pressure Determinations by the Auscultatory Method," in which he presents the results of an investigation of the errors in judgment involved in reading the blood pressures by the auscultatory criteria. He finds the error in judgment to be less than in the case of the oscillatory criteria. In reply to the results therein recorded I wish to say now that in observations made by my students under conditions as objective as it is possible to make them, the agreement between the systolic readings as made by the "change in form" criterion and the auscultatory criterion is exact to the pulse wave, while for the diastolic pressure it is exact to within two or three pulse waves.

1 As a matter of fact, the auscultatory method was not generally accepted until it was shown that its readings agreed in general with those of the oscillatory method, while the auscultatory phenomena have received their explanation through experiments in which readings of the oscillatory and auscultatory methods have been compared.

curtail the use of this method, or to cast doubt on recorded results obtained by it, it is my duty to avail myself of the opportunity so considerably afforded of replying to Dr Kilgore's criticisms. At first I had hoped to do this in a constructive way, by gathering for my reply new data with special reference to the points raised by Dr Kilgore. Unfortunately, however, the press of other work has rendered the preparation of such a reply impossible at this time. I hope, though, that I may soon have the opportunity of presenting such data. In the meanwhile I must content myself with a criticism of Dr Kilgore's methods based on logic and on past experience with blood pressure methods.

II

In the first place let me say that while Dr Kilgore's results demonstrate beyond peradventure that the determinations of the blood pressure by the *continuous escapement* modification of the oscillatory method, when not checked by well-known procedures, obviously may give rise to much confusion and uncertainty, it should nevertheless be borne clearly in mind that the method of intermittent escapement, a more definite, though slower, procedure than the method of continuous escapement and the one that was used when this subject was in the experimental stage, is not here the subject of discussion. The object of this reply is to point out the pitfalls that may be encountered in the use of the method of continuous escapement and the way to minimize them. At the same time it will be necessary to indicate some places where, in our opinion, Dr Kilgore might with advantage have employed slightly different methods in approaching his problem.

Dr Kilgore maintains that by his method of procedure the discussion of his results is limited to certain topics only, that these do not include "the general question of sources of error in blood pressure measurements," or the "truthfulness of the oscillatory indices, once they are accurately identified."

I am perfectly willing to submit to this limitation of the discussion if Dr Kilgore, on his side, is ready to maintain that his records were made and controlled under the best of conditions, or even under conditions that ordinarily should obtain in routine observations. The fact that he included in his critique only such records as were read without question by those to whom they were submitted, does not, for reasons to be given below, materially modify our consideration of this point.

Let us then examine Dr Kilgore's methods. With the Erlanger sphygmomanometer he made a large number of tracings, over 1 300, recording simultaneously with the oscillations by means of a mercury

manometer the pressure in the cuff as it was gradually falling² We are led to suppose that no earnest endeavor was made to interpret these records until all had been made. In other words Dr Kilgore must have assumed that the process of reading a blood pressure record is similar to the process of reading ideal instruments of precision, for instance, the scale of a galvanometer which is being deflected by a steady current. In doing this he has failed to realize two important considerations: (1) he has failed to realize that the blood pressure criteria, like the end-points of volumetric chemical determinations, can be altered with respect to distinctness through changing conditions, and (2) he has failed to realize the significance of the personal factor as affected by his particular methods.

(1) Blood pressure criteria are not equally clear under all circumstances. When they are not clear it is usually possible, by means of slight changes in the adjustment of the apparatus, for example by changing the magnification of the oscillations by simply shifting the tambour in or out, to bring them out with unmistakable clearness. Furthermore, the form of the record may be materially altered by the variable conditions under which they must be made. If proof of variability in form is desired, it is only necessary to inspect the records published by Dr Kilgore. Among them can be found at least a dozen different types. With the change in type, the criterion one is accustomed to look for may be difficult to recognize. Now if one finds on reading a record that he is in doubt as to the points he should select as indicative of the pressures he is seeking to determine, the attempt should then and there be made to redetermine the "end-points" by making a record by the method of intermittent escapement. I can assert that in the vast majority of instances the difficulty can by this procedure be made to disappear. If not the method of intermittent escapement alone should then be used.

Dr Kilgore's failure to appreciate these facts has presumably gotten him into his dilemma. Without ever stopping to determine whether his end-points were clear, and, if not, whether they could be made so, he has proceeded to make long series of records. He then finds, when the time arrives to read his records, that many of them seem to be illegible. On consulting others he finds that while some essay to read

² I am inclined to believe that the larger mercury manometer that must be used if the fall of pressure is to be recorded by a float, on account of its greater oscillation and greater mass, will have a tendency to eliminate the characteristic criteria of the oscillatory record.

most of the records without question (of this more later), others hesitate to read any ³

I do not by this discussion mean to give the impression that it is possible in every case to obtain clearly the criteria for reading the pressures. Rarely, however, when at first there is difficulty in finding the marks, is it impossible to obtain, by slight readjustment of the apparatus, criteria that give perfectly clear and consistent readings.

We may therefore conclude that while Dr Kilgore's records may represent the kind that one is often called on to read in practice, there are reasons for believing that if he had used the procedure which it is advisable to employ in practice, he would have secured clearer records and consequently more consistent readings.

(2) These records were then submitted to a number of observers with the request that they mark the "satisfactory ones." By discarding those not marked, as well as those marked but questioned, Dr Kilgore believes that he has removed from consideration all records which, through faulty technic or accident, are not up to standard, or conversely that the records marked were entirely satisfactory and as good as those ordinarily made. We have already given reasons which indicate that Dr Kilgore did not obtain as clear records as it is possible to get. The fact, however, remains that these records were marked and that there was no agreement among the different observers as to which records were satisfactory and which unsatisfactory.

In connection with these facts it is necessary to examine into the psychology of a problem of this kind.

(a) Is it not legitimate to ask in this connection "Would the same persons have accepted without question similar records made in the course of their own work? Is it not possible that the critical attitude, with which one is in the habit of interpreting results he is in a position to control for himself, might have been warped by the request to "mark the records?"

(b) Furthermore, when readings are made, on the one hand, by one whose whole soul is in the investigation, and, on the other, by one who is asked to make the readings as a favor, and who, therefore, takes only a casual interest in the affair, there can be no question as to which of the two sets of readings will be the more dependable. When, in addition, one who is not directly interested has the task set him of carefully selecting two points on each of 100 records, a matter which,

³ For example see Henderson's letter. I agree in large part with Henderson's criticism, for I, too, found it impossible to read many of the tracings with any degree of certainty (Consult Dr Kilgore's paper). The results of my two attempts to indicate the diastolic pressure, showing an average difference of only 5.4 mm of mercury, prove that the diastolic pressure index, even in these blindly made records, is not so indistinct as Henderson thinks it is.

if properly done, will consume a not inconsiderable part of a working day, it is obvious that the personal factor must become unusually large. An excellent example of the significance of this factor is to be found in the data submitted by Dr Kilgoie. "E" says, "I have chosen the first apparent maximum oscillation without making measurements of the tracings"⁴ Yet it is perfectly obvious on mere inspection of "E's" marks that he has not selected the highest oscillations. So impressed am I by his inconsistencies that I cannot refrain from directing attention to at least a few of them.

No of Record	Amplitude of Oscillations	
	Marked by "E"	Maximum [*]
	mm	mm
5	18	20
6	17	19.5
12	29	32
16	24	27
58	16	19
63	20	25
65	20	24
78	22	24
88	24	27
91	28	33

*I have not the information needed to determine in millimeters of mercury the differences between "E's" oscillations and the maximum oscillations. It is obvious, however, that it is not inconsiderable.

I do not, by this exhibit, mean to imply that "E" (whose identity is unknown to me) is an incompetent observer. I present it merely for the purpose of showing that disinterested opinion may often be of questionable value. There is no possibility of controlling in the same way the readings of the other observers, since the criteria they use are not definite enough for this purpose. If this could have been done I am inclined to believe that similar inaccuracies would have become evident. It might be maintained that this is purely and simply the personal factor that enters into all observations rather than the error resulting from disinterestedness. However this may be, if it could be convincingly maintained that "E's" readings represent the error involved in picking out the highest oscillations on a record and under the very best of conditions, I must confess that my faith in the data of "observers" would be rudely shaken, and I would then be inclined to suggest that we give up in despair our efforts to develop quantitative methods in medicine in general and in sphygmomanometry in particular. If relative amplitudes of recorded deflections cannot be judged, what confidence can we have in judgments based on a change in intensity of a sound or of an impact on the finger?

⁴ This, by the way, is not the accepted criterion of the diastolic pressure.

(c) The factor of judgment may next be considered. We have already referred to the fact that the sphygmomanometer record cannot be read in the same way as can a deflection on the scale of a galvanometer. The continuous escapement record does not present a steady crescendo to and then beyond the systolic mark nor a steady diminuendo beyond the diastolic mark. Rather we have superimposed on these a series of wave-like variations in amplitude, some regular, and due to the respirations, and some irregular.⁵ So difficult it is on this account to locate the first sudden increase in amplitude that I have altogether discarded the use of that criterion in connection with the method of *continuous escapement*, and now judge the position of the systolic pressure by the "change in form" alone.

Be this as it may, it is obvious that when the criterion is the sudden increase in amplitude a double judgment is necessary. Such error as has resulted from this double judgment could have been minimized only by having placed at the disposal of the observers several records obtained from the same individual at the same sitting and under as nearly as possible the same conditions. In such records the systolic and diastolic changes in amplitude would have fallen in different phases of the respiratory waves and could then the more readily have been dissociated from them. A part of the variation in the readings of the several observers undoubtedly is due to their not having had at their disposal this legitimate aid to the formation of a judgment.

Nevertheless, it is obvious that many of the discrepancies in the readings of the different observers are too wide to receive their explanation in this way alone. As Dr Kilgore points out in this connection, the trouble in part lies in not knowing the end-point to be looked for.

(d) Dr Kilgore's study has also brought out some anomalous "judgments" which we hesitate to refer to because of the standing of the observers whose marks form the basis of the criticism. Since, however, Dr Kilgore lays so much stress on the absence of agreement as to which records are satisfactory, I cannot refrain from asking just one question that may help to throw some light on the difficulty. I would like to know how "F" would justify his diastolic mark in Record 13? This he places without question in the midst of an irregularity obviously due to motion of the arm. While this is the most flagrant instance of this kind still there are many others to which the same criticism applies. It should be added, however, that if "F" had had

5 These waves are more marked in Dr Kilgore's records than in those made in this laboratory. It would consequently seem that he did not observe as carefully as is possible the usual precautions to avoid the motions of the arm on the chest that occur in association with respiratory movements.

the opportunity of observing this record while it was in the making he would probably have recognized the cause of its fault

Is it not possible, in view of the fact that a certain amount of judgment must be employed, that one investigator may regard as unsatisfactory a record acceptable to another, that the former may recognize, say, a disturbing respiratory wave which the latter fails altogether to take into consideration? Obviously, therefore, if each observer had had at his command a second record, or better, a series of records from the same subject made at one sitting and the opportunity of discarding inconsistent readings, there would have been a closer agreement on the question of readability of the tracings

III

When I first saw Dr Kilgore's records I stated that it was practically impossible in most instances to make use of the criterion of the systolic pressure, which I have designated the "change in form," because his drum had not moved fast enough. This criterion, it might be added, is by far the clearest and sharpest of the systolic criteria, in fact it is practically the only one that I now use. The speed that is necessary to bring this criterion out clearly is a relative matter, though in general it may be said that the criterion increases in clearness directly as the speed of the drum, which in Dr Kilgore's experiments was not fast enough, and inversely as the magnification by the lever, which in most of Dr Kilgore's tracings was greater than was necessary

IV

Dr Kilgore is quite right in insisting that if two criteria are actually indicative of the same thing, they must occur with the same pulse wave. Increase in amplitude⁶ and the change in form should and do coincide in the vast majority of cases when they are clear. My experience convinces me that they fail to affect the same wave only through accident to the recording mechanism. It can, though very rarely, happen that as a result of vibration or draughts or roughness of the paper or what-not the lever does not press on the drum evenly throughout its entire excursion. It may happen that during the very wave that marks the systolic pressure the lever meets, say with increased friction, so that, while the change in form becomes manifest, the amplitude of the oscillation is not increased. As a matter of fact, the very record that Dr Kilgore uses for the purpose of illustrating the lack of correspondence of the criteria gives clear evidence of the operation of some one such factor as the disturbing element, the lever here fails to sink to the general level of the record

⁶ The increase in amplitude often is not clear

V

With regard to the "puzzle" of submitting two sets of the same records to the same person for his opinion as to the location of the systolic and diastolic criteria, the results obtained, in view of what goes before, are "more interesting than conclusive"⁷ The result was, however, very much as I had anticipated rather wide discrepancies in the case of the systolic pressure, and fairly close average agreement in the case of the diastolic pressure The discrepancy in the case of the systolic readings I expected would be large because the tracings "were not made on a surface that was moving with sufficient speed to bring out satisfactorily the change in form" The average error of 5.4 mm of mercury in the case of the diastolic readings is no larger than the error inherent in the method itself, it is, therefore, well within the requirements of the method The insignificance of this error can be made clear when it is pointed out that if in one reading the prick had been made just one pulse wave above a given pulse wave, and in a second reading just one pulse wave below the same wave, the error would, in many instances at least, have been practically 5 mm of mercury Greater accuracy than this is not to be expected in the present state of our knowledge And when it is recalled that this good average was made in spite of certain wide discrepancies, amounting to as much as 17 mm of mercury, obviously due to the disturbing influence of the respiratory waves, discrepancies which I am certain would not have occurred if we had had at hand the means we always have in practical sphygmomanometry of using only the consistent readings, one, I think, must be struck by the surprising agreement of the two sets of readings, rather than by the few instances of disagreement

VI

In reply to Dr Cabot's casual remark in regard to the unreadability of the diastolic pressure as indicated by the oscillatory method (for it is this rather than the reading by any specific instrument that he, undoubtedly, has reference to), I desire to make these remarks (1) Even under the unfavorable conditions of Dr Kilgore's test I succeeded in finding in both of two attempts thirty-two records that I thought were legible as regards diastolic pressure, and these I succeeded in reading with an average difference of 5.4 mm of mercury Evidently even under these circumstances, the records are not entirely unreadable (2) Would Dr Cabot care to maintain that the many investigators who, in comparative tests, have found the oscillatory

⁷ Quotation from my letter to Dr Kilgore at the time the second set of records was marked

criteria of the diastolic (and the systolic) pressure to agree, as well as could be expected, with the auscultatory criteria, could not or did not read their records? A more conservative statement, and one with which every one could agree, would have been that they are often unreadable. As I have previously said this could not be otherwise, because the blood pressure is not an immobile affair from which clear and identical records can be obtained time over and again. Rather, as a result of the play of the various blood pressure waves that is constantly going on during the period required in all methods for the determination of blood pressure, it is obvious that many of the readings by the method of *continuous escapement*, though by no means all, must inevitably be illegible. (3) Furthermore, I would like to know whether Dr. Cabot means to include in his sweeping condemnation, the readings made by means of the method of *intermittent escapement*.

Dr. Janeway's "opinion" with regard to methods of determining the blood pressure in the part of the artery subjected to compression loses its force completely in view of the fact now frequently recorded that the auscultatory and oscillatory criteria of the systolic pressure agree very closely, in my own experience, let me repeat, the agreement is exact. (See footnote at beginning of article.)

In conclusion let me say that I hope my remarks will not be taken as an attempt to discredit Dr. Kilgore's method of attacking the problem in hand, or of the conclusions he has reached. My main purpose has been to show (1) that those records that were sufficiently clear were read alike (within the limit of experimental error) by the same observer in two successive trials, (2) that the discrepancies appearing in the readings of different observers are probably greater than they would have been if each had been given the opportunity of making the records for himself under conditions obtaining in routine work, and (3) that our present criteria are by no means discredited by Dr. Kilgore's studies. But over and above all of this stands out the fact brought out by Dr. Kilgore, that without proper controls, readings of blood pressure records made by the method of continuous escapement may be, if not carefully made, worthy of only slight consideration.

The remedy would seem to lie (1) in using as the systolic criterion the change in form, with the paper moving at sufficient speed for this purpose, (2) in using the first *consistent* decrease in amplitude as the index to the diastolic, and (3) when in doubt, in controlling the readings made by the method of continuous escapement by readings made by the method of intermittent escapement.

It is regrettable that the only objective criteria we possess are sometimes difficult to make clear, and can be read only by exercising a certain amount of judgment. But until better objective methods can be

found, a goal toward which we are constantly striving, we must do the best we can with available methods though they may be fraught with large, in part known, inherent errors. These remarks, it may be added, apply with equal force to all methods now practiced of determining the blood pressure in man, for the record obtained by the graphic method is the resultant of all of the forces, both external and internal, acting to produce any of the criteria, and while some criteria may be clearer than others, they all are affected in much the same way by the changing forces. The nongraphic criteria may seem to be changed less but from experience I can affirm that this is almost entirely the result of our inability to gauge the less objective criteria.

By observing proper precautions I am convinced, from my own experience, that the oscillatory criteria will be found to be quite as clear and as sharp as the auscultatory criteria, while the former possess the advantage, that is not without its value, of bringing to the attention of the observer the deficiencies of our blood pressure methods in *black and white* rather than in the form of *opinions*.

A QUANTITATIVE DETERMINATION OF THE PERSONAL FACTOR IN BLOOD PRESSURE MEASUREMENTS BY THE AUSCULTATORY METHOD

COMPARISONS WITH OTHER METHODS [†]

EUGENE S KILGORE, HUGH K BERKLEY,
ALBERT H ROWE AND W H STABLER
SAN FRANCISCO

Much has been written with regard to errors in human blood pressure measurements connected with such factors as rigid arterial walls, a too narrow cuff, etc., or the choice of the criteria for determining when pulse waves begin to pass under the cuff or when the diastolic pressure is reached, but heretofore little attention has been paid to the personal factor which operates in the identification of the various criteria. Since it is the large amount of individual judgment involved in "guessing" blood pressure by feeling of arteries, which has led to the general adoption of instrumental methods, it is important to inquire, in addition to other sources of error, how large this personal element may be when blood pressure instruments are used. Oscillatory criteria both for systolic and diastolic pressure, which have been advocated for use with several highly authorized instruments and which have been widely accepted as the most accurate and freest from subjective error, have been shown to invite surprisingly large variations in interpretation.¹ The ordinary palpatory method for systolic determinations has been investigated from this point of view² and the present report deals with similar experiments applied to the auscultatory criteria for both systolic and diastolic pressure. The experiments were in three groups.

GROUP 1—The "Two-Arm" Experiments. This group consists of experiments by two of us (K and S) on sixty-one candidates for admission to the university, all healthy young men from 16 to 32 years of age. During the course of the required medical examination the blood pressure determinations were made with the subject lying quietly on his back on a narrow table. A 12 cm. pneumatic cuff was fitted to each arm, and both cuffs were connected with the *same* mercury U-tube manometer, which was overhung so as to be equally readable from both sides of the table. Both cuffs were inflated simultaneously.

[†] From the Department of Medicine and the Students' Infirmary, University of California.

1 Kilgore, E. S. Page 893, this issue.

2 Kilgore, E. S. California State Jour. Med., March, 1914.

to a pressure above systolic pressure, and then, while the air from the combined system was gradually released through a slow outlet valve (the mercury falling about 2 mm per second), one of us listened with a small open bell stethoscope over the artery a few centimeters below the cuff on the right arm while the other with a similar stethoscope ausculted at a corresponding point on the left arm. Each independently recorded by his reading of the manometer when the first sound was heard (systolic pressure), when the loud tapping sound finally changed to a dull distant one (the so-called "fourth phase" index of diastolic pressure), and when all sounds were lost ("fifth phase" index of diastolic pressure).³ After two such procedures on one side we changed sides and repeated. Whenever the reading was not clear on account of extraneous noise or other accident no result was recorded, but if the observation was unhindered and the reading not clear on account of doubt about the definiteness of the criterion, a question mark was recorded in place of the reading. In these as well as in later experiments care was taken to avoid unconsciously signaling to one's partner when readings were made.

In this group the differences between the simultaneous readings of two observers obviously may be due to two causes. 1 Differences in hearing and interpreting the sounds and in observing the corresponding positions of the mercury column. 2 Actual differences in the blood pressure in the two arms or differences in the size or position of the artery or in the adjusting of the cuffs and stethoscopes. In order to separate these factors and ascertain the discrepancies referable to each of them the following group of experiments was undertaken.

GROUP 2—The "One Arm" Experiments. In this group of experiments by K. and S., sixty-six of the same class of subjects were utilized. The procedure was exactly the same as in the first group with the exception that only one pneumatic cuff was used and but one stethoscope with a Y connection and two pairs of ear pieces. With the two branches of the stethoscope tube of equal length and the manometer equally readable to both observers, it is evident that both made their readings from absolutely identical data and that the discrepancies occurring in this series are referable solely to the first cause mentioned.

3 Discussions of the merits of these "phases" as indices of diastolic pressure will be found in the following articles: Korotkoff, *Mitth. d. med. Akad. zu St. Petersburg*, 1905, xi, 365; Fischer, *Ztschr. f. diätet. u. phys. Therap.*, 1909, xii, 389; Lang and Mansivetona, *Deutsch. Arch. f. klin. Med.*, 1908, xciv, 441; Ettinger, *Wien. klin. Wchnschr.*, 1907, xvi, 992; Gittings, J. C., *Auscultatory Blood-Pressure Determinations*, *THE ARCHIVES INT. MED.*, 1910, vi, 196; Warfield, Louis M., *Studies in Auscultatory Blood-Pressure Phenomena*, *THE ARCHIVES INT. MED.*, 1912, x, 258.

above The discrepancies due to the second cause may then be determined by subtracting these results from the former ones

GROUP 3—The Control "One-Arm" Experiments These were repetitions of the last group of experiments undertaken by the other two of us (B and R) as a control for the experiments of K and S The essential sameness of the results in the second and third groups counts toward the justification of the assumption that our results would correspond reasonably with those of others—an assumption formerly made by two of us in considering our results with the palpatory method² The subjects in this group were twenty patients in the medical and surgical wards of the University of California Hospital They were of both sexes and varied in age from 14 to 53 years and were without obvious cardiovascular abnormality They were resting quietly on narrow hospital beds, and the manometer, which was a straight mercury tube and reservoir, was placed on a shelf over the bed As an additional precaution against one observer's influencing the other, in these experiments a screen was placed over the bed between them, and the inflation and deflation of the cuff was controlled by an assistant

To facilitate comparisons and avoid bewildering columns of figures, the results have all been reduced to percentages and expressed graphically in Figures 1 to 9 The curves are all according to one plan, which is to show the discrepancies between the readings of two observers⁴ expressed in millimeters of mercury, and the percentage of instances in which each degree of discrepancy occurred Millimeters of mercury are expressed along the abscissae and percentages of instances along the ordinates Each curve except in Figure 7 extends both to the right and to the left of zero in order to show separately for each observer the instances in which his readings were the higher Thus, a curve with long, lateral extensions and a blunt peak indicates that there were some large discrepancies and relatively few agreements, while a sharp tall peak with short lateral extensions signifies comparatively good results A curve which reaches its highest point away from the zero pressure ordinate indicates a general tendency for one of the observers to choose higher reading points than the other Perfect results would be represented by a peak reaching to 100 per cent at zero mm Hg

In the first and second groups of experiments, in which a U-tube manometer was employed, there was a tendency for the readings and, hence, the discrepancies, to fall on the even numbers oftener than the odd, thus giving the plotted curve a "saw-edge" outline Since irregu-

⁴ In one instance (Fig 9) the marks of one individual made at two different times on duplicate graphic records are compared, and in Figure 7 the "fourth phase" and "fifth phase" readings of the same observers are compared

larities of this dimension, when once their cause is recognized, have no further importance but interfere somewhat with the larger comparisons which it is desired to make, they have been "smoothed out," as will be observed, by combining values for the even and odd millimeters of mercury

In the experiments in which the one divided stethoscope was used (Groups 2 and 3) the practical correspondence of the results by two pairs of observers is shown in Figures 1, 2, and 3. The solid lines show the differences between the readings of K and S and the dotted lines the same for B and R.

In the systolic determinations (Fig 1) the differences in the second group vary from zero to 12 mm Hg and average 1.42, in the third group from 0 to 10 mm Hg, average 1.58.

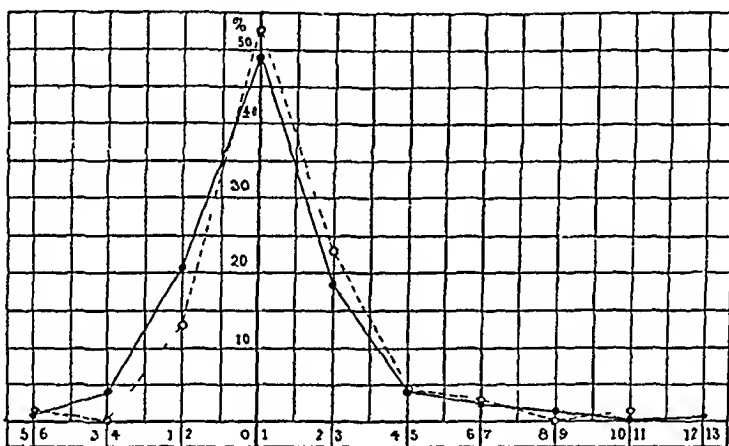


Fig 1—Close correspondence shown in results of two series of "one-arm" systolic readings. Solid line, discrepancies of K and S, dotted line those of R and B. The cases in which K's readings and those of R were higher than those of their partners are to the left side, to the right are the cases in which S's and B's readings were higher.

In the use of the change of sound or "fourth phase" diastolic criterion (Fig 2) discrepancies in the second group occur as high as 15 mm Hg and average 2.6, in the third as high as 9 mm Hg, average 2.47.

In locating the points of sound disappearance (Fig 3) K and S recorded points as far apart as 17 mm Hg, and their average difference was 2 mm, B and R had an average difference of 1.76 mm Hg and once 10 mm.

It will be seen that there is essential uniformity in the results of the two pairs of observers both in the range and distribution of the discrepancies and in the averages. In view of this correspondence it is assumed that the showings made by K and S in the first and second groups of these experiments, as well as in their previously

reported experiments with the palpatory method² represent the errors referable to the personal factor which ordinarily prevail in the use of these methods. In the following analysis, therefore, only their results are included.

The Systolic Readings—Taking as we did, as the index of systolic pressure, the first sound heard while air was escaping from the cuff, none of these points was classed as doubtful in any of the series of experiments. The beginning of the sounds was usually very clear cut,

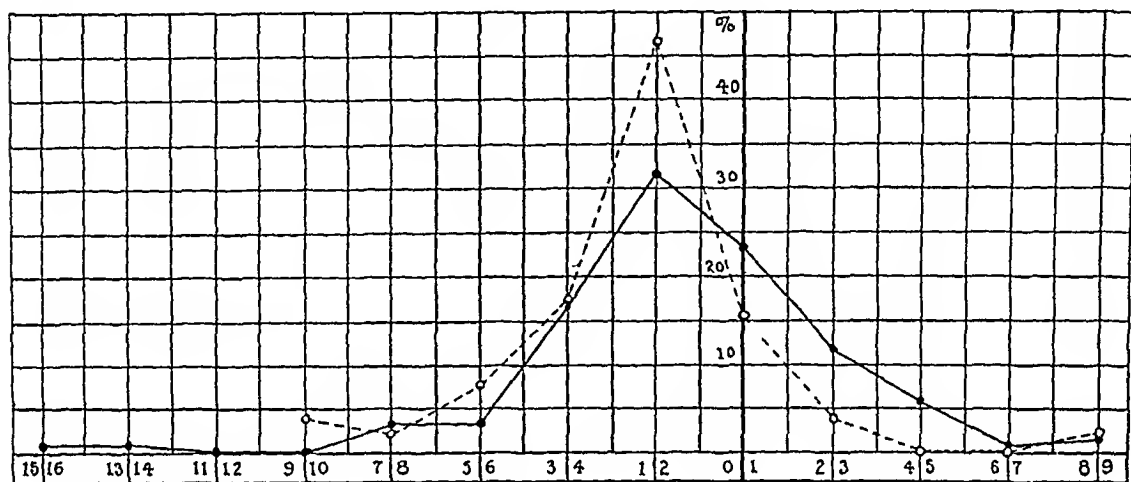


Fig 2—"Fourth phase" diastolic readings. Arrangement same as in Figure 1, except that the higher readings of B are to the left and those of R to the right.

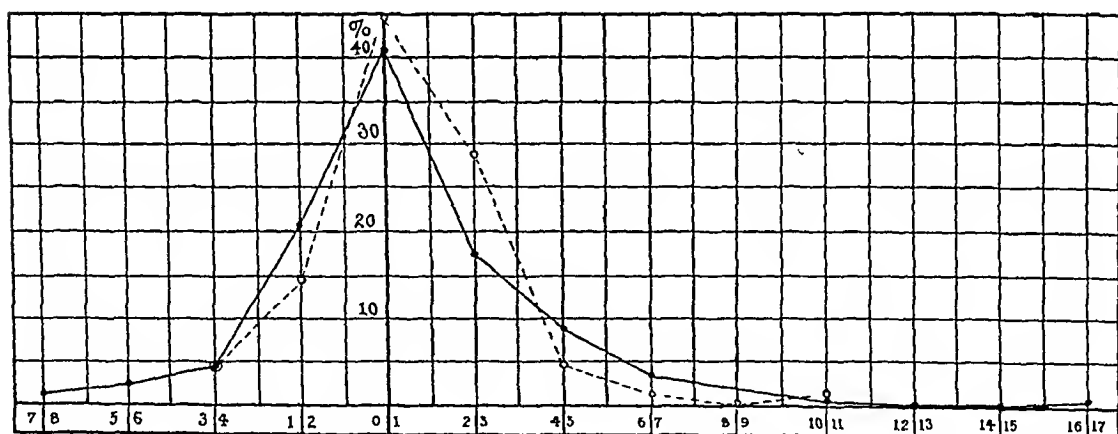


Fig 3—"Fifth phase" diastolic readings. Arrangement same as in Figure 1.

and we were surprised by some of the large discrepancies in our records. It seems probable that some of the wide variances here as well as in the diastolic determinations were due to mistakes of ten points in reading the manometer.

As previously indicated, disagreements in the second group of experiments in which but one cuff and one stethoscope were used can only be accounted for by errors in reading the manometer and in recognizing the criterion. These are shown in the solid line in Figure

4 The dotted line shows the discrepancies of the same observers when two pneumatic cuffs and two stethoscopes were used The figure shows that in the "two-arm" experiments fewer of the discrepancies are near zero and more of them have higher values than in the "one-arm" group, the average in the former case being 3.54 mm Hg and in the second 1.42 The difference of 2.12, as explained above, is a measure of the added effect of using both arms of the subject and applying two cuffs and two stethoscopes

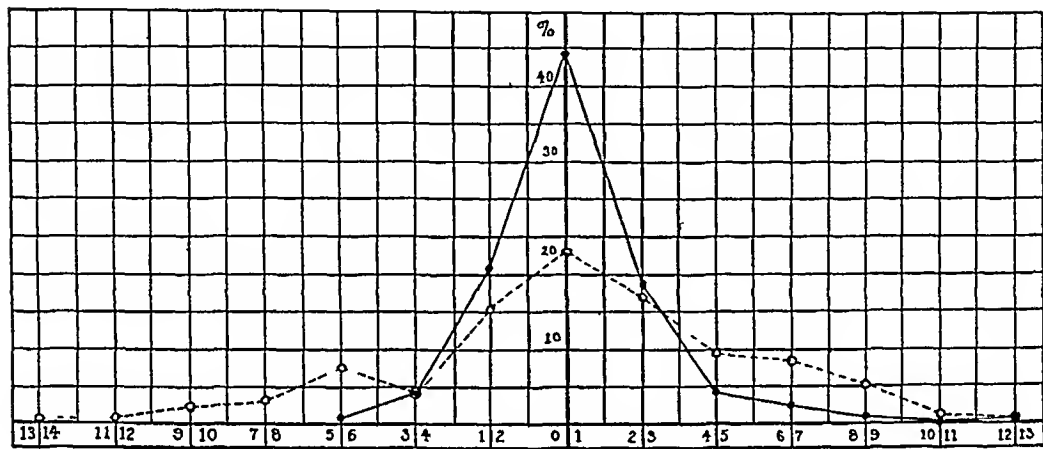


Fig 4—Systolic readings Relation shown between discrepancies in simultaneous readings of K and S using one stethoscope (solid line) and the discrepancies of the same observers in the "two-arm" experiments (dotted line) The higher readings of K are to the left, those of S to the right

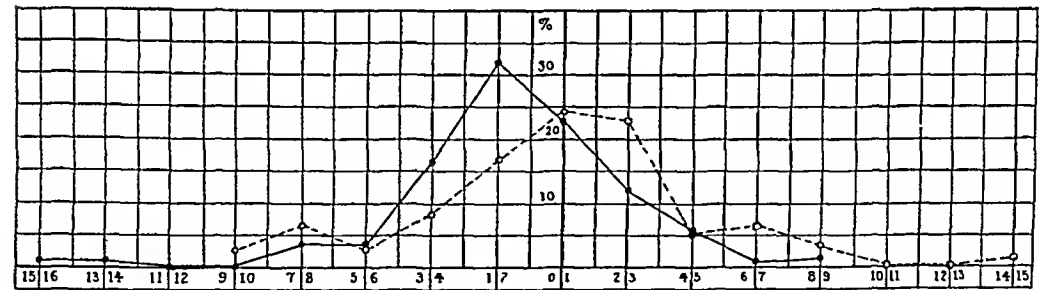


Fig 5—"Fourth phase" diastolic readings "One-arm" and "two-arm" determinations compared as in Figure 4

These figures are based on 236 determinations (by each of two observers) in the sixty-one subjects of the first group, and 282 determinations on the sixty-six subjects in the second group None of the readings were classed as doubtful

The Diastolic Readings by the "Fourth Phase" Index—Figure 5 is arranged in the same way as Figure 4 to show the comparative results when one stethoscope and when two were used The average discrepancy in the one-stethoscope experiments was 2.6 mm Hg, in the

first group 3 09, a difference of 0 49 mm Hg. The smallness of this difference is partly explainable by the tendency of K in the second group of determinations to choose a point 1 or 2 mm higher than S did, a tendency not observed in the first group of experiments and clearly due to a slight change during the course of the experiments in the habit of either S or K in interpreting the criterion.

Out of 232 attempted "fourth phase" readings in the first group only seventy-nine were accepted for the above analysis, the remaining 153 (66 per cent) being classed as "doubtful." These occurred in fifty-five of the sixty-one subjects. Similarly among the 273 attempted readings in the second group 143 or 51 per cent (occurring in fifty-seven out of the sixty-six subjects) were rejected as "doubtful."

"Fifth Phase" Diastolic Readings—In the first group there were 228 of these readings and in addition four marked questionable; in the second group 260 readings and twelve which were discarded as doubtful.

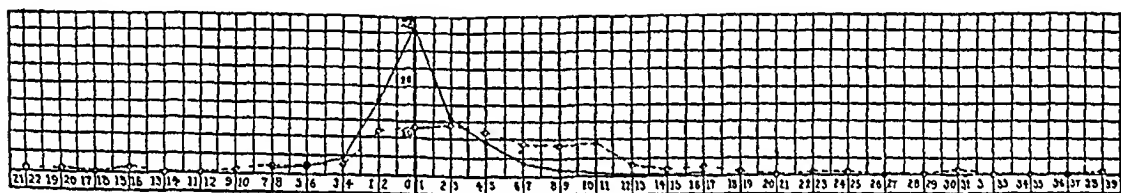


Fig 6—"Fifth phase" diastolic readings "One-arm" and "two-arm" determinations compared as in Figure 4

Figure 6 shows that in the one-stethoscope experiments the results are comparable with those for the other criteria, and that the two observers took the higher readings about equally.

In the "two-arm" experiments the discrepancies are much larger than usual on both sides of the figure, which suggests that in these subjects at least the disappearance of sounds is particularly subject to variation from sources other than blood pressure, such, for example, as anatomic variations or variations in the adjustment of the apparatus.

The curve also shows, however, that a preponderance of the higher readings was made by S, that is, K more often followed the sounds to a lower level. Since this difference does not appear in the "one-arm" experiments, the only possible explanation is that here again, during the course of the experiments, one at least of these observers changed his habit of interpreting the criterion.

Relation Between "Fourth Phase" and "Fifth Phase" Readings—An opportunity is here afforded to compare the difference between "fourth phase" and "fifth phase" readings in two slightly different groups of subjects, hospital patients and young men students. Figure

7 shows this comparison in the two groups of experiments which were exactly parallel (the "one-arm" experiments) on the two classes of subjects. In each group the readings of both observers have been included, the solid line represents the differences between fourth and fifth phase readings when the students were used as subjects by S and K, the dotted line represents the same differences in the readings of B and R on hospital patients. It will be noted that the greatest differences between these two diastolic indices occurred among the deter-

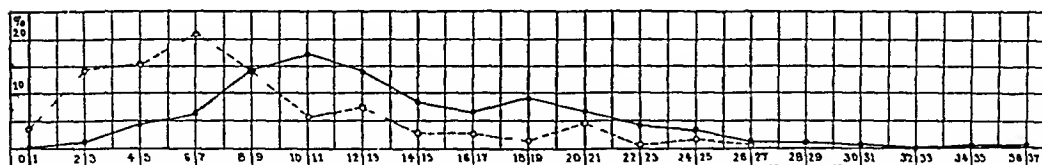


Fig 7—Relation shown between "fourth phase" and "fifth phase" diastolic readings in the "one-arm" test of K and S on students (solid line) and of B and R on hospital patients (dotted line)

minations on students, the average difference was considerably higher in this group, 13.5 mm Hg as compared with 8.5 mm Hg in the measurements on hospital patients. In a few instances the two indices were so near together as to be practically inseparable.

COMPARISON WITH OTHER METHODS

A The Palpatory Method. For systolic blood pressure, the conditions affecting the "two-stethoscope" experiments in this series were practically identical with the conditions in the palpatory systolic

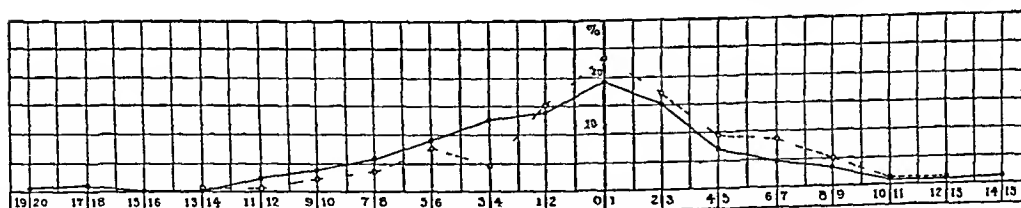


Fig 8—Systolic readings. Close correspondence shown between the discrepancies of the palpatory method (solid line) and the auscultatory method in the "two-arm" determinations of the same observers. The cases in which K's readings were higher are to the left, those of S to the right.

measurements previously reported for the same two observers,² so that the two methods may be directly compared. This comparison is shown in Figure 8, the solid line representing the discrepancies of K and S with the auscultatory method and the dotted line the same with the palpatory method. The figure shows that although the auscultatory discrepancies in the region of zero have a slightly higher percentage and never on the extreme sides of the curve quite equal the largest

palpatory discrepancies, still the differences are relatively small and well within the limits of experimental variation. In fact, in view of the tendency illustrated above for observers from time to time to change their habits of interpreting the criteria, these two curves approach coincidence as nearly as could be expected if either of these groups of experiments were repeated. The difference between the average discrepancies (3.54 mm Hg in the auscultatory and 4.08 mm Hg in the palpatory) is small in comparison with other variables in series as small as these.

We have not investigated the personal factor in the use of Strassburger's palpatory diastolic criterion, as it seemed hopelessly great.

B. The Oscillatory Method. In another article¹ experiments are being reported concerning the personal factor in the interpretation of the oscillatory criteria. The conditions of those experiments do not permit an exactly parallel comparison with our tests of the auscultatory and palpatory methods, the nearest that can be made is with the "one-arm" auscultatory tests, in which the conditions are favorable to the oscillatory indices in four respects: (1) The personal factor connected with the reading of the manometer is not included in these oscillatory results. Further, in contrast to the conditions of actual practice, the oscillatory readings were made (2) on completed tracings, (3) without the need for haste, and (4) without the necessity of dividing the attention between them and the manometer.

The two subjects whose descriptions of the oscillatory systolic criterion seem most alike are "A" and "D." In seventy systolic readings which escaped criticism or expression of doubt by either of them their differences range from zero to 20 mm Hg and average 2.91 mm Hg, which, it will be remembered is about twice the average discrepancy in either of the two series of "one-stethoscope" experiments. In view of the conditions, previously mentioned, it is to be presumed that this average would be materially increased in actual practice by these observers, and the comparative showing made by them is decidedly unfavorable to the sudden increase in amplitude or "principle of von Recklinghausen," which they followed. That the ordinary palpatory index of systolic pressure would stand with the auscultatory criterion in the same favorable comparative light if it could be subjected to the "one-arm" test may be assumed from the close correspondence which we found to exist between it and the auscultatory method in the "two-arm" experiments.

The "change in form," the other systolic oscillatory criterion proposed by Erlanger,⁵ is not included in these comparisons, because the

⁵ Erlanger, Joseph. *Am Jour Physiol*, 1908, *xxi*, 24.

evidence concerning the personal factor in its use was not considered conclusive Also Erlanger's method of "intermittent escapement"⁶ for systolic and diastolic determinations was not the subject of experiment

In the second part of the article on the oscillatory indices referred to above the average discrepancy in a series of diastolic comparisons is 5.4 mm Hg, which, it will be remembered, is approximately two or three times as great as the average for either fourth or fifth phase determinations in both of our groups of "one-arm" experiments (fourth phase discrepancies of K and S averaged 2.6 mm Hg, of B and R 2.47, fifth phase discrepancies of K and S 2, of B and R 1.76) We have taken our worst showing, the "fourth phase" readings of K and S for comparison with these oscillatory diastolic discrepancies, the dotted line in Figure 9 represents the oscillatory results, the

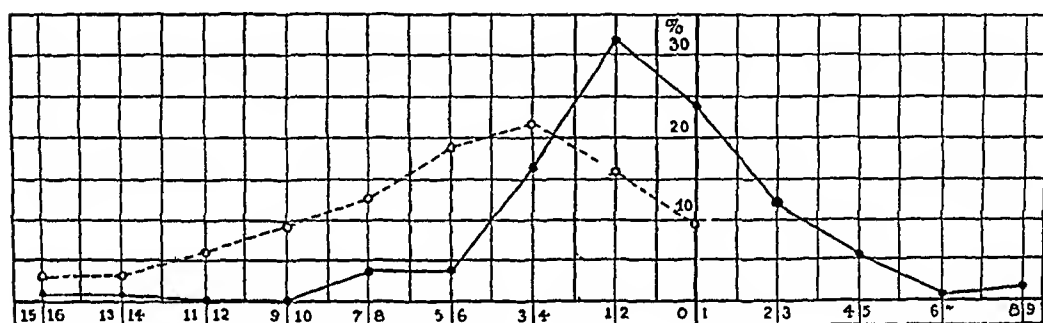


Fig 9—Diastolic readings "Fourth phase" auscultatory discrepancies in K's and S's "one-arm" experiments (solid line) compared with discrepancies in rereading by the same observer ("C") diastolic points in graphic oscillatory records (dotted line) K's higher readings are to the left The cases in which C's later readings were higher than his earlier ones are charted to the left The dotted line does not appear to the right, as earlier readings were never higher than the later ones

solid line the auscultatory In judging this comparison it must be borne in mind that the oscillatory readings were performed under the four conditions of unnatural advantage mentioned above, that is, conditions which are not enjoyed in practice Moreover, in this instance, the oscillatory method was favored in another and specially important item in that the marks of but one individual ("C") instead of two were compared—an advantage which is possible only to graphic records, and which was obtained by submitting for marking a second series of photographic prints of tracings identical with a series which had been marked by the same observer eleven months previously

Figure 9 also shows a pronounced change of habit in interpreting the oscillatory diastolic criterion on the part of "C," his higher readings without exception being found on the second set of tracings

DISCUSSION AND CONCLUSIONS

These investigations are practically limited in scope to a single source of error in blood pressure measurements, namely, personal differences between observers in the identification of auscultatory systolic and diastolic criteria and in reading the mercury manometer. In the "two-arm" experiments, however, anatomic causes of discrepancies or actual differences in blood pressure between the two arms of the subjects could not be ruled out.

So far as our experiments go, there is little to choose in point of definiteness between the common palpatory systolic index and the newer auscultatory criterion. Our findings, therefore, while not including tests of a sufficient number of observers to be conclusive, do not substantiate the impression widely existing at present that the stethoscope offers a much more definite and reliable systolic blood pressure index than that formerly used. While it is not within the scope of this paper to consider at length the relative merits of methods, it may be pointed out that an intelligent choice between the auscultatory and palpatory methods for systolic readings will involve consideration of the following points: (a) the convenience of the palpatory method, (b) its freedom from interference by extraneous noises, (c) the fact that most of the blood pressure data in clinical literature refer to the palpatory method, (d) the fact that in certain subjects the auscultatory readings cannot be made, and that in certain others they are lower than can be obtained by palpation, (e) the fact that, whereas the auscultatory readings are commonly higher than the palpatory, the latter themselves have been found to be somewhat too high in the few instances in which they have been controlled in human subjects by direct manometric measurements.⁷

The commonly used oscillatory indices, according to our analyses, invite much greater vagaries in interpretation than either the palpatory or auscultatory method for systolic readings or the auscultatory for diastolic readings.⁸ This finding, if it receives confirmation, will be particularly important in view of the wide acceptance of the

7 Muller and Blauel. *Deutsch Arch f klin Med*, 1907, xci, 517, Volhard *Verhandl d Cong f inn Med*, 1909, xxvi, 200, Dehon, Dubois and Heitz *Compt rend Soc de biol*, 1912, lxxii, 789.

8 Part of the discrepancies in the use of the oscillatory method were attributable to individual differences in the understanding of the criteria to be followed. This factor, we believe, has not appreciably influenced our results with the palpatory and auscultatory methods. The palpatory systolic criterion used by some, however, is the "fully developed" radial pulse wave rather than the first one to be felt. An index which depends on the relative amplitude of pulse waves is obviously much less definite than the appearance of a wave where none before existed, and for this reason as well as because it is the more commonly used criterion, we have accepted the first wave to be felt, although certain theoretic considerations favor the fully developed waves.

oscillatory method as the most "objective," hence the freest from personal factor errors, and its use on this account as a standard or means of "checking up" other methods. Reasons have been presented¹ for the special condemnation of methods in which the attempt is made to use the oscillatory indices with instruments which do not supply graphic records.

Notwithstanding their favorable comparison with the oscillatory method, both of the auscultatory diastolic criteria which have been proposed leave much of definiteness to be desired. This is shown in our "fourth phase" determination by the large number of readings which were rejected because the sound changes were not considered abrupt enough to afford clear readings, as well as by the comparatively large number of higher discrepancies in the comparisons which were made.

Our greatest differences in simultaneous readings occurred in the "fifth phase" experiments, in which, in one instance, we differed by as much as 38 mm Hg. Particularly in our "two-arm" experiments the number of instances in which we agreed was small. These results we believe would have been modified decidedly for the better if all our subjects had been of the ordinary hospital class. For, in examining the students, who as a rule are more or less excited by the novelty of the medical examination, we have been impressed with the unusually gradual and protracted waning of the artery sounds before their final disappearance. In accord with this impression is our finding of a considerably greater average difference between the fourth and fifth phase readings in the student measurements than in those made on hospital patients. Our experiments on the students indicate better agreement among the fourth phase determinations than in the fifth phase, in the experiments on hospital patients, however, the fifth phase determinations showed a slightly smaller average discrepancy.

In conclusion it should be stated that the differences between blood pressure readings in these experiments would be somewhat lessened if as a basis for comparison the highest reading by each observer on a case or the average of several readings were used, instead of individual readings. Better results might also be obtained by combining methods, using one as a check against another. The comparison of single simultaneous readings, however, while it makes for ourselves a somewhat poorer showing than we may hope exists in our actual practice, is the direct way to determine disagreements of observers, and it is obviously the best way to compare results obtained by different methods.

THE FRACTIONAL METHOD OF BLOOD PRESSURE DETERMINATION—A CONTRIBUTION TO THE STUDY OF BLOOD PRESSURE IN CARDIAC ARRHYTHMIAS *

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Among the sources of error in human blood pressure measurements an important factor, which has received comparatively little attention, is variation in pressure between individual pulse waves or between groups of them. It is well known that undulations in systolic and diastolic pressure occur commonly in normal persons with each respiration or at somewhat longer intervals, and among the cases of cardiac arrhythmia, there may be the widest pressure differences even between consecutive pulse waves. The custom of clinicians to accept the average or the highest of several determinations, or simply the first reading made, while tolerably meeting the needs of practice among cases with regular heart action, amounts to the roughest kind of guess-work in cases of marked arrhythmia. Mackenzie¹ gave up the attempt to measure blood in cases of auricular fibrillation. It will be shown, however, that notwithstanding the great differences between individual waves in these cases, the average pressure from minute to minute may be remarkably stable, and that the determinations, though not expressible as single figures, may have as much accuracy as the ordinary clinical methods will yield in normal cases.

It will be unnecessary here to discuss the numerous attempts which have been made to obtain graphic records showing quantitatively the rapid changes in human arterial pressure. Suffice it to say that up to the present the sphygmographs and plethysmographs used as receivers have been beset with technical difficulties which make them not only inconvenient, but uncertain in their results.²

Another group of endeavors has had more limited aims, such as

a To show the highest and lowest systolic pressures in a series of irregular beats, by noting the cuff pressure at which no beats come through and that at which all come through.³

* From the Department of Medicine, University of California

1 Mackenzie Heart, 1911, 11, 283

2 Weber Arch f Anat u Physiol, 1913, Physiol Abt

3 Wybauw Ztschr f klin Med, 1911, lxxiii, 214

b To show qualitatively variations above or below a known systolic pressure by noting the appearance and disappearance of the "change in form" in an Erlanger sphygmomanometer curve ⁴

c By the method of intermittent escapement and the use of the graphic oscillatory criteria, to show the general level of systolic and diastolic pressures when there is variation among the beats ⁵

d To compare the number of beats coming through one radial artery with those coming through the other when varying degrees of pneumatic pressure are applied to one arm, using a sphygmograph on each wrist for registering the beats ⁶

Observations similar to the last mentioned were made by James and Hart,⁷ but without the use of instruments other than the ordinary clinical blood pressure apparatus. Their method was to count the heart rate by auscultation of the precordia, and by palpation of the radial artery the rate without arm compression and also with different degrees of compression by the pneumatic cuff. From these observations they could state approximately (1) The number of beats per minute which fail to reach the periphery as palpable waves (the so-called "pulse deficit"), and (2) the number per minute which have a systolic pressure of 140 mm Hg, 130, 120, and so on ⁸. The pressure variation among the pulse waves in the arm they designate the "relative deficit". What they call the average pressure is obtained by multiplying, for example, by 140 the number of beats per minute which they considered to have that pressure, by 130 the number with that pressure, and so on, then adding all these products and dividing the sum by the heart rate as counted at the apex. They did not apply the procedure to diastolic pressures.

A simple method such as this is attractive on account of the non-requirement of machinery other than the ordinary blood pressure apparatus. The only advantages which could be claimed for one of the graphic methods would be the doubtful one of increased accuracy in identifying and counting the waves which passed under the compressing cuff, and the possibility of registering simultaneously the rate of the unobstructed pulse. The pulse rate would, of course, be needed for correct interpretation of the results if it changed materially from minute to minute. That such is not the case, however, in cases of auricular fibrillation, where this method finds its greatest usefulness, is the experience of James and Hart and of myself. Moreover, in the

4 Erlanger and Festerling *Jour Exper Med*, 1912, xv, 370

5 Erlanger *Johns Hopkins Hosp Rep*, 1904, xii, 53

6 Silberberg *Brit Med Jour*, April 6, 1912

7 James and Hart *Am Jour Med Sc*, January, 1914, p 63

8 A slight error in these calculations will be referred to later

method of plotting the results here proposed, any noteworthy change of the pulse rate or of the general run of pressure during the experiment would at once become evident as a distortion of the curve. The essential "smoothness" of such a curve is evidence of the constancy of the circulatory conditions during the experiment.

A method differing from that of James and Hart in two important particulars (the interpretation of systolic determinations and the inclusion of diastolic readings) was initiated in the University of California Hospital about one year before their publication, and the illustrations herewith presented are taken from the hospital records of the last two years. We have designated it the *fractional method* because of its obvious similarity to the fractional procedures of chemistry, bacteriology, etc. It will best be described by examples.

Section 1—Cases in which the Lowest Systolic Pressures are Above the Highest Diastolic Pressures. Medical Case 8243, admitted Nov. 13, 1914, diagnosis, mitral stenosis, auricular fibrillation. Although the heart was absolutely irregular, practically every beat had a corresponding radial pulse. With circular compression of 150 mm Hg applied by a 12 cm pneumatic cuff to the upper arm, no waves were felt in the radial artery of the same side during half a minute. After emptying the cuff and resting the arm a few seconds, the pressure was again raised and held for one half minute at 145 mm Hg. During this time two waves were felt at the wrist. Then there was another rest of the arm, inflation of the cuff, and half minute count of the waves which were able to lift 140 mm Hg, and so on down to 110 mm Hg, which obstruction all the waves were able to pass.

For the fractional determination of diastolic pressure a stethoscope was placed over the artery a few centimeters below the cuff, and with further similar decrements of cuff pressure, the numbers of arterial sounds heard in half minute intervals were counted (i. e., the "fifth phase" or sound disappearance criterion was followed).

The results are shown graphically in Figure 1, in which the dots represent the rate per minute (indicated by the corresponding figures on the base line) of waves which pass under a given degree of pressure in the pneumatic cuff (indicated by the corresponding figures at the left), and where the circles in a similar way indicate the counts of sounds. The connecting lines, it will be noted, are drawn with the purpose of representing the probable truth rather than with absolute faithfulness to the dots and circles. i. e., *small* irregularities have been "smoothed out." This undoubtedly increases the accuracy of the lines (provided of course that enough counts have been made to bring the

dots and circles approximately in line), since it is what happens when such curves are based on much larger numbers of counts. The purpose of this paper being primarily to describe the method, in the interest of clearness and simplicity in the figures which follow only the smoothed out lines are shown

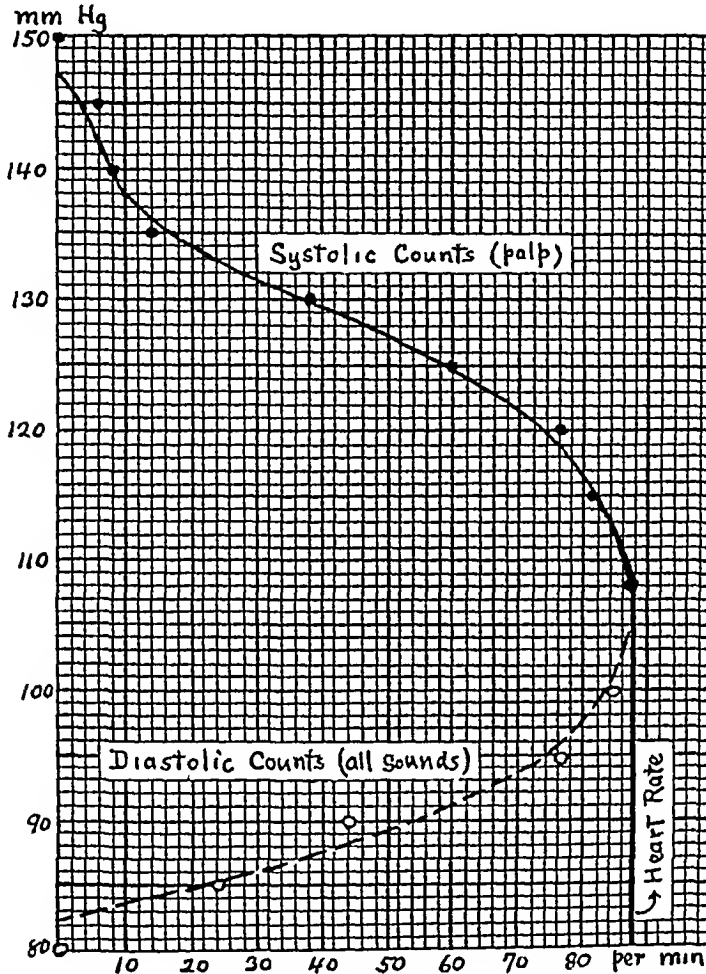


Fig 1—Showing the relation of systolic and diastolic pressures in a typical case of auricular fibrillation in which the diastolic pressure of one cycle never exceeds the systolic pressure of another. In this as well as the following figures the numbers at the left indicate millimeters of mercury pressure in the pneumatic cuff, those at the bottom the rate per minute of beats counted in various ways. The upper line here represents the results of palpatory systolic counts, the lower line fifth phase diastolic counts.

Figure 1 may be better understood if it is imagined that the 88 pulse waves in a minute are represented by sticks with lengths proportional to the systolic pressures, and that these sticks are stood up in the order of their lengths, the longest on the left and the shortest on the right. Their tops would form the upper curve in the figure. A similar set of sticks representing diastolic pressure would form the lower curve if the longer ones were placed on the right.

It will be seen that the systolic pressure varies between 110 and 145 mm Hg, and that its average is in the neighborhood of 125 to 130. To continue the illustration of the sticks, the average systolic pressure would be represented by their average length, which would be obtained by dividing the sum of their lengths by their number. The average length of 88 equally spaced ordinates dropped from the systolic curve in Figure 1 is about 129.

An approximately correct average can be obtained with less labor by dealing with groups rather than points on the line representing single waves. For example, according to the figure, there were six waves per minute with a pressure between 145 and 150. These six may all be considered to have a pressure half way between the two limits, i. e., 147.5 mm Hg. In this way the complete calculation would be as follows:

(a)	(b)	(c)*	
6—	0=	6	$6 \times 147.5 = 885$
8—	6=	2	$2 \times 142.5 = 285$
14—	8=	6	$6 \times 137.5 = 825$
38—	14=	24	$24 \times 132.5 = 3,180$
60—	38=	22	$22 \times 127.5 = 2,805$
76—	60=	16	$16 \times 122.5 = 1,960$
82—	76=	6	$6 \times 117.5 = 705$
88—	82=	6	$6 \times 112.5 = 675$

$$11,320 - 88 = 1286 = \text{average systolic pressure}$$

*In the figures shown herewith the numbers on the base line correspond to the figures in column *a* in the above tabulation, i. e., they represent total numbers of waves felt or sounds heard at the corresponding cuff pressures. For some purposes it would be an advantage to construct curves in which the base line figures represented the quantities in column *c*, i. e., the number of beats which have a certain pressure. In such a figure taken from a normal case there would be two narrow curves separated by the amount of the pulse pressure, while if it were from a very irregular case the diastolic and systolic curves might overlap. The work of constructing these additional curves is unnecessary if it is remembered that their lateral extent would depend on the slope of the curves here employed. In the figures herewith, the more uniform the pressure of the beats the more nearly horizontal the lines, and the more variable the pressure the more sloping the lines.

It will be noted that this average differs by only about one-half millimeter from that obtained by measuring the whole 88 ordinates. In the averages calculated by James and Hart⁷ only half as many multiplications were made, i. e., waves were considered together which were within limits 10 mm Hg apart instead of 5 mm. Undoubtedly the additional error introduced in this way is still well within the limits of accuracy of the method as a whole. A mistake of approximately 5 mm Hg, however, appears throughout their figures, which is unnecessary and easily corrected. For example, a group of beats which ranged in pressure from 130 to 140 mm Hg they counted as

having a pressure of 130. On the chances, the average pressure of this group would be near the midpoint or 135 rather than the lower limit of 130.

The diastolic pressure is calculated from the lower curve in Figure 1 in the same way as systolic pressure, thus

(a) (b) (c)*

24 — 0 = 24	$24 \times 82.5 = 1,980$
44 — 24 = 20	$20 \times 87.5 = 1,750$
76 — 44 = 32	$32 \times 92.5 = 2,960$
84 — 76 = 8	$8 \times 97.5 = 780$
88 — 84 = 4	$4 \times 102.5 = 410$

$$7,880 - 88 = 89.5 = \text{average diastolic pressure}$$

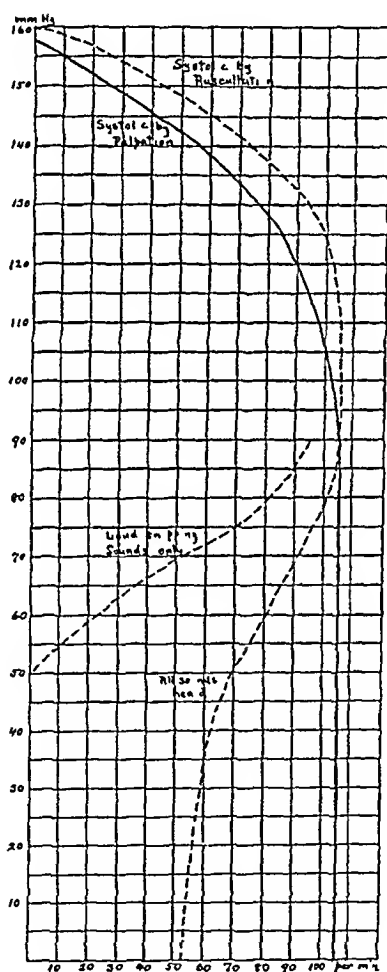


Fig 2—Showing the relation between palpatory (solid line) and auscultatory (broken line) systolic readings, and between fourth phase and fifth phase diastolic readings. From a case of hyperthyroidism and auricular fibrillation.

Obvious variations of the technic are to use the auscultatory method for systolic determinations and the "fourth phase" or sound transition index for diastolic readings, i. e., to count all the arterial sounds heard instead of the pulse waves felt in the systolic region, and in the diastolic region to include in the counts only the loud staccato notes and omit the dull distant ones. Figure 2 shows

side by side the results obtained by the use of the palpatory and auscultatory criteria for systolic pressure, and of sound transition and sound disappearance for diastolic pressure. It will be seen that in these fractional determinations there is present the usual excess of auscultatory over palpatory systolic readings, and of "fourth phase" over "fifth phase" diastolic readings. The case from which this was obtained was one of auricular fibrillation with hyperthyroidism. The pulse approached the Corrigan in type, which accounts for the persistence of many of the arterial sounds during little or no cuff pressure.

For purposes of comparison it is desirable to use the same criteria for the determinations in these cases of arrhythmia as in ordinary cases. For general use in systolic determinations our choice has been the palpatory criterion, on account of its convenience, and we believe, equal or greater reliability¹⁰. For diastolic readings we ordinarily use whichever auscultatory criterion seems the clearer, and indicate in the record which is used. In fractional determinations the "fifth phase" criterion is usually preferable, as it relieves the observer of the necessity of differentiating between qualities of sounds, and also takes away the danger of confusing sounds above the "fourth phase" with those below it. (In the second and third phases the murmur is frequently indistinct and the sounds very dull and distant.) A few cases, such as aortic insufficiency, will have audible sounds over the arteries with little or no compression; these necessitate the use of the sound transition criterion. Unless otherwise stated it is understood that the remaining observations here referred to were all obtained by the use of the palpatory index for systolic pressure and the disappearance of sounds for the diastolic.

Section 2—Cases in which the Diastolic Pressure of Some Beats Exceeds the Systolic Pressure of Others. Figure 3 (Case 9229, May 21, 1915) illustrates this condition. Instead of coinciding as in Figure 1, the lines representing, respectively, systolic and diastolic pressure intersect; i. e., apparently the diastolic pressure of some cycles exceeds the systolic pressure of others. When this is so, it is necessary to make certain allowances in interpreting the diastolic counts with the higher cuff pressures, for the reason that not all of the silent waves are so because their diastolic pressures are above that in the cuff, some are not heard because they fail entirely to pass the cuff. An example in Figure 3 is the count of sounds when the cuff pressure was 115 mm Hg. The figure shows that the rate of these sounds was 58 per minute, which would mean, according to the

¹⁰ Kilgore. A Quantitative Determination of the Personal Factor in Blood Pressure by the Auscultatory Method, *THE ARCHIVES INT MED*, this issue, p 893

usual interpretation, that fifty-eight waves per minute had a diastolic pressure lower than 115 mm Hg. But from the palpatory systolic counts it is known that even less cuff pressure was able to hold back entirely some of the smaller waves (at least so far as the finger could determine), and therefore, wrongfully for our results, exclude them from the stethoscope counts. The upper end of the diastolic line, therefore, needs to be corrected by bending it toward the right.

To determine the amount of correction to be made in the diastolic line, it is first necessary to make some of the systolic readings by auscultation as well as by palpation and to correct the lower end of the auscultatory systolic line (where beats may be missed on account of high diastolic pressure as well as on account of low systolic pressure) in accordance with the palpatory readings, i. e., so that the vertical

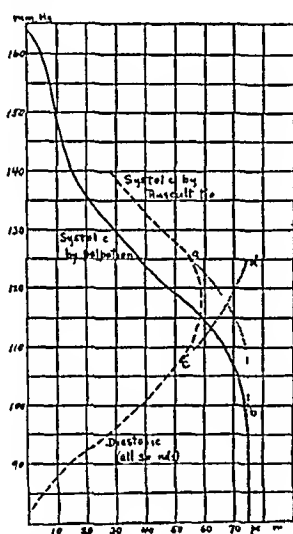


Fig 3—Showing the correction and extension of the upper end of the diastolic line in cases in which the diastolic pressure of some cycles exceeds the systolic pressure of others. Case of premature contractions followed by alternating pulse waves.

distance between the two lines shall be everywhere the same as at the higher pressure levels.¹¹ The dotted portion (*ab*) of the systolic auscultatory line in Figure 3 has been thus corrected. The difference between each point in this corrected auscultatory systolic line and the heart rate per minute, equals the number of waves per minute which are silent at that cuff pressure on account of their lower systolic pressures, and is therefore the number of beats to be added in order to correct the diastolic line at the corresponding pressure. For example,

¹¹ It is assumed that the relation between palpatory and auscultatory systolic readings is about the same at different pressure levels. This probably is not strictly true, but it is certain that any error from this source is small and well within the limits of accuracy of the method as a whole.

at pressure 110 this corrected auscultatory systolic line indicates 72 per minute, which is three short of the heart rate of 75. Three beats are therefore added to the diastolic line at pressure 110. Similarly at 115, five beats are to be added, and so on. The dotted portion (*cd*) of the diastolic line in Figure 3 was constructed in this way.

From these corrected lines the average systolic and diastolic pressures may be calculated as described in Section 1. The cases in which it is necessary thus to correct the diastolic line are comparatively few, as even in very marked cases of arrhythmia the diastolic line does not intersect the systolic line until both are at or near their limit. And when they cross only slightly before this, the diastolic line can be roughly corrected by "free hand extrapolation" within the limits of accuracy of the method.

Section 3—Cases in which without Brachial Compression Some of the Heart Beats Fail to Reach the Radial Artery as Palpable Waves
Cases with abortive beats¹² form a large proportion of the patients with absolute arrhythmia in the stage of decompensation, and a considerable number of patients with premature contractions. Clinically there is no method at present of measuring the exact pressure of these small beats, but they can be placed between certain rough limits. Those which produce both first and second heart sounds may be assumed to have opened the semilunar valves¹³ (presumably both pulmonic and aortic), and therefore to have exceeded the diastolic pressure of the preceding beat. Isolated first heart sounds, on the other hand, may be taken to indicate beats with systolic pressure below the existing diastolic pressure in the aorta.

Unfortunately the diastolic pressure as a limit is itself quite variable in most of these cases (in Figure 3, for example, it varies from 82 to 125 mm Hg). Since, however, a prominent factor in causing

12 The difference between the apex and the radial counts has been referred to as the "pulse deficit." "Abortive beats" has seemed to us a better term because its meaning is clear and it directs attention to the heart, in respect to which these beats are important, rather than to the pulse, where they are not so important. Even in the presence of many abortive beats, there may be an ample number of large beats for the needs of the peripheral circulation, and from this point of view it seems not quite appropriate to speak of the small beats as a deficit. Indeed they might with less impropriety be referred to as a surplus.

13 Professor Joseph Erlanger has verbally called my attention to the possibility of second heart sounds occurring without a preliminary opening of the semilunar valves. It is quite conceivable that the systolic pressure—on the side of the ventricle may at times be sufficient partially to relax the tension on the valves without opening them, and that their return to the tense position at the beginning of diastole may produce a sound. Whether or not this actually takes place would of course be difficult to prove, if it does, the sounds thus produced might be expected to be less intense than the second sounds of the effective beats.

these small ventricular discharges (or attempted discharges) is insufficient ventricular filling, due to the shortness of the preceding diastole, and since it is usually the long pauses that bring about the low diastolic pressures, it may be inferred that these abortive beats usually happen during relatively high diastolic pressure. Occasionally, particularly in some cases of premature contractions, several small beats follow each other in rapid succession, the output of these beats may be negligible, and arterial pressure during the short interval may therefore decline rapidly, and the last beat or two may fall in instants of relatively low diastolic pressure. If desired, a cardiographic record or a record of

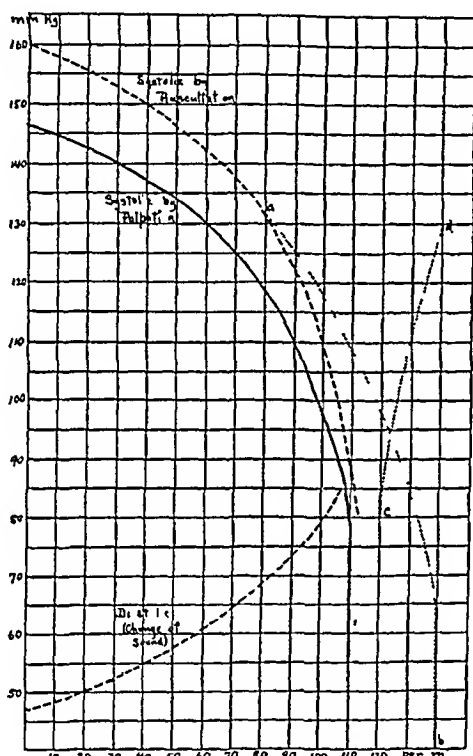


Fig 4—Showing the correction of the lower end of the systolic line to represent abortive beats. Hyperthyroidism with auricular fibrillation

heart sounds could be used for studying the diastolic periods and the probabilities that a certain proportion of the beats would occur during high or low diastolic pressure.

Figure 4, which is from a case of myocarditis with premature contractions (No 7747), shows that with a cuff pressure of 80 mm Hg all the waves were felt which could be felt with no cuff pressure (110 per minute), and yet each minute there were thirty additional heart beats which could not be felt at the wrist, but which, the sounds were assumed to indicate (second sounds always present), discharged blood into the aorta against a diastolic pressure of 50 to 80 mm Hg. And, since these abortive beats did not occur in series, it may be assumed that the systolic pressure of the weakest of them

was probably over 65 mm Hg. Moreover, it is highly probable that their pressures varied as did those of the larger beats, and that, therefore, if measurable they would be represented by a line approximately in the position of the dotted line *ab* in Figure 4, i e., a continuation of the auscultatory¹⁴ systolic line by a more or less symmetrical curve up to the full heart rate (140) and the presumable pressure of the weakest beats (65 mm Hg). Fortunately, in the region of low pressure this curve is naturally bending so little that the exact location of the point of lowest systolic pressures, which, as explained above, is quite conjectural, makes comparatively little difference in the placement of the line.¹⁵

14 The fact that systolic readings by palpation are usually somewhat lower than those by auscultation presumably indicates that the auscultatory method is more delicate for determining the pressure of waves which can pass the cuff. And, since in this rough calculation of the pressure of the abortive beats naturally no margin is allowed for failures to demonstrate them, the line representing them should be a continuation of the auscultatory rather than the palpatory systolic line.

15 The line *ab* representing the systolic pressure of the abortive beats in Figure 4 extends up as high as 130 mm Hg. A natural question will be why beats with such a pressure cannot be felt in the radial artery with no brachial compression. It is a frequent observation that patients with systolic pressure as low as 50 or 60 mm Hg (shock, etc.) have distinctly palpable pulse waves. The answer of course is that the palpability of pulse waves depends not on their absolute pressure, but on the relative increment of pressure, which in turn depends very largely on the volume discharged from the ventricle. That is, with suitable allowances for distensibility of artery walls, interference of surrounding tissues, etc., the case comes under Weber's psychological law (Wagner's Handwörterbuch, Braunschweig, 1846, III, Abt 2, p 511), which is to the effect that for equal increments of sensation, increasing increments of stimulation are necessary. The small pressure increments presumably also prevent many beats with high absolute pressure from giving rise to sounds below the cuff.

The line representing abortive beats in cases other than absolute arrhythmia may obviously have a different type of curve, depending on the conditions. For example, in a case with regular effective beats and regularly recurring abortive premature contractions, the latter might all have about the same pressure, so that they would have to be represented by a nearly horizontal line. In order to locate a rough limit for the pressure of the abortive beats, it would be necessary, as in the case illustrated by Figure 4, to determine the diastolic pressure which they did or did not exceed (presence or absence of second sounds). This could be done approximately by comparing the electrocardiogram or record of heart sounds with an absolute sphygmogram from the case prepared according to the method of Sahli (Diagnostic Methods, 1911, p 174). The time interval between the abortive beat and the preceding effective beat when marked off on the absolute sphygmogram would indicate, within the limitations of the method, the diastolic pressure at the instant of the abortive beat.

The line *ab* in Figure 4 may be used according to the directions in Section 2 for constructing the upper end of the diastolic line. Line *cd* was constructed in this way. It will be realized that this corresponds to the results, which if it were possible, should have been obtained by the use of the fifth phase criterion. This accounts for the fact that the line *cd* does not join with the main diastolic line of the figure, which, on account of the water-hammer character of the pulse, it was necessary to obtain by the use of the fourth phase criterion.

The fractional method here described may with propriety be used in many cases other than auricular fibrillation to demonstrate and to measure blood pressure lability, for example, the range of Traube-Hering waves or respiratory waves of blood pressure, of sinus arrhythmia, premature contractions, alternating pulse, etc. Figures 5, 6 and 7 are given as examples

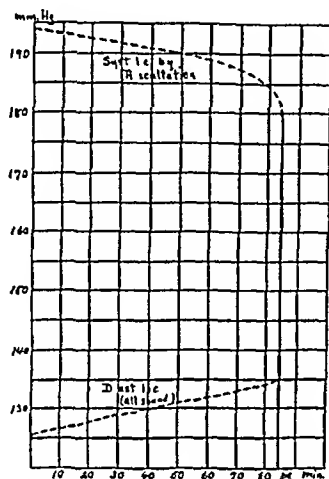


Fig 5—Showing a slight amount of pressure lability in an apparently pressure-stable case Nephritic hypertension

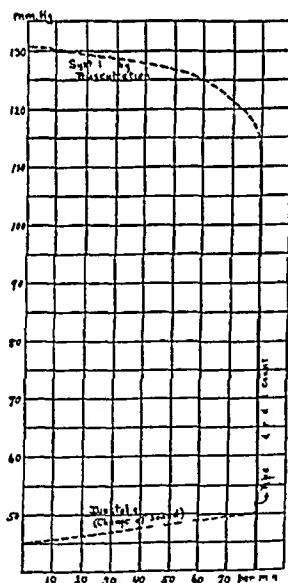


Fig 6—Showing a moderate amount of systolic pressure lability due to Cheyne-Stokes respiration Aortic insufficiency

Figure 5 is from a case (No 6220) of nephritic hypertension in which with ordinary examination the pressure seemed stable. The fractional method shows a variation of 5 or 10 mm Hg in both systolic and diastolic measurements.

Figure 6 is from a case (No 6397) of aortic insufficiency in which a moderate amount of systolic variation is attributable to Cheyne-

Stokes breathing (Longer counts may be necessary to obtain smooth curves in cases in which the pressure undulations are as slow as in Cheyne-Stokes breathing)

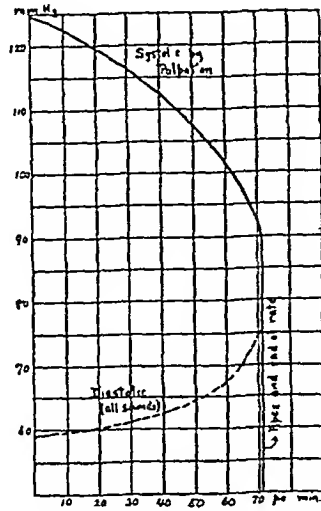


Fig 7—Showing much variation of systolic and diastolic pressure due to respiratory arrhythmia

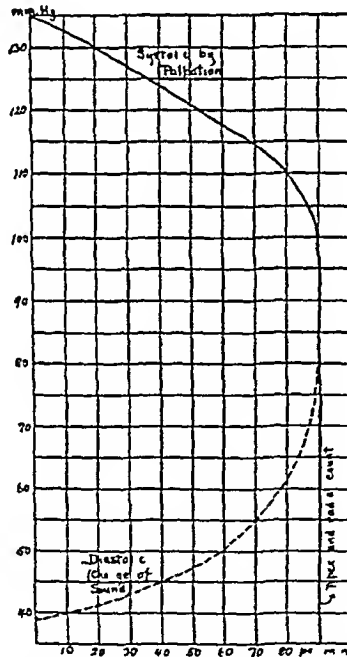


Fig 8—Showing a large average pulse pressure as compared with systolic and diastolic pressures in a case of aortic insufficiency with auricular fibrillation

Figure 7 is from a marked case of respiratory arrhythmia in a boy aged 11 (Case 9680, seen by courtesy of the surgical service) Both systolic and diastolic variability is practically as great as in some of the cases of auricular fibrillation

DISCUSSION

The Practical Application of Fractional Blood Pressure Determinations It is the habit of many clinicians to think of blood pressure as a quantity connected with a patient almost as definite and stable as his

body weight, or at least as his temperature. Clinical writers who discuss, for example, changes of 5, 10, 15, or 20 mm Hg following certain therapeutic procedures, do not as a rule give sufficient weight to the probable latitude of error in the actual determinations or to the many causes of pressure fluctuations over short time intervals. And even when it is realized that in a case of absolute arrhythmia each pulse wave has a different pressure, the inclination is to combine them into a mean or average figure or to take the pressure of the highest beats, and to attach to these figures the same significance that is carried by the measurements in ordinary cases.

It is hoped that the method here described and the figures used for illustration will help to counteract this tendency, and to emphasize first of all the limitations of human blood pressure determinations.¹⁶ Figures 5 and 6 illustrate, respectively, cases of slight and moderate pressure variability in which in the ordinary run of clinical work some one figure for each case would be reported as the blood pressure. From this as well as from observations on the personal factor of observers,¹⁰ it would seem necessary that unusual precautions be taken before reliable inferences can be drawn from small differences in blood pressure.

In the frankly pressure-labile cases further precautions are demanded. Both the amount and the kind (shape of the curve) of pressure variation should be taken into consideration. Average systolic and diastolic pressure can always be calculated from the results of the fractional determinations, after correcting the plotted curves when necessary, as described in Sections 2 and 3. And, with the possible exception of the cases with abortive beats, these averages, based as they are on many observations, may be expected to be as accurate as the usual measurements in normal cases, and probably more so. And in the many instances in which the pressure variation is only moderate and all heart beats produce palpable waves, they undoubtedly bear a fairly close relation to the measurements in pressure-stable cases so far as the usual clinical interpretation of these figures is concerned, i. e., they may be used as indices of hypertension or hypotension, of changes in blood pressure, etc.

The problem is different when many abortive beats are present. If these are included in the calculation, the resulting "average pressure" may have little practical relation to ordinary blood pressure figures. To illustrate. A patient with regular pulse, rate 65 per minute, and systolic pressure 140, is found to have a regularly recurring premature contraction immediately after each effective heart beat, so that

16 I have reviewed the general question of sources of error in blood pressure determinations in the *California State Journal of Medicine*, 1914, xii, 92.

the heart rate is really 130. The absence of some of the second sounds and the weakness of others belonging to the abortive beats presumably indicates that their systolic pressure is in the neighborhood of the diastolic pressure of the large beats, which is 80 mm Hg. They cause such small pressure increments, however, that they cannot be felt, and they are negligible so far as the effectiveness of the circulation is concerned. It is obvious that in any consideration of blood flow, vaso-motor control, etc., the pressure and the rate of the large beats alone should be taken into account, while the abortive ones would have a separate significance as dissipators of heart energy.

The same is true in cases of premature contractions or auricular fibrillation where the abortive beats are interspersed irregularly. But in these cases there may be every grade of transition between the effective and the abortive beats. The threshold of palpability is a convenient criterion which we have used for distinguishing between the "effective" and the "abortive" groups, and the average pressure of all the beats which can be felt at the wrist may have a somewhat close relationship to the usual measurements in pressure-stable cases. It should be remembered, however, that the distinction at this point is an arbitrary one, and that beats just above the threshold may not have a value for the peripheral circulation proportional to their pressure, while beats just below the threshold may have some value. The highest waves, on the other hand, may not have an efficiency commensurate with their pressure, for the reason that the high pressure is not sustained. Since the ventricle throws out a large volume of blood almost as quickly as a small one,¹⁷ the rapidity of outflow varies according to the volume of the discharge, and with it also the inertia or "hydraulic ram" action of the blood stream. The latter may run up the instantaneous pressure out of all proportion to the efficiency of the wave.¹⁸ That is, the same care should here be taken that is necessary in interpreting ordinary blood pressure readings in such cases as aortic insufficiency.

For the reasons given above, the "average blood pressure" of James and Hart,⁷ which includes without distinction the abortive beats, seems to us to be misleading. Certainly for most purposes it is preferable to calculate the average systolic pressure from the palpable beats alone and to give the abortive beats separate consideration.

But if for any cause it is desired to use the general average of both classes of beats, the method of James and Hart would need modification, because it fails to take any account of the pressure of the abortive beats. Since these authors made no use of the method of plotting

¹⁷ v Frey and Krehl. *Arch f Anat u Physiol*, 1890, p 31

¹⁸ Erlanger and Hooker. *Johns Hopkins Hosp Rep*, 1904, xii, 145

results here described, and did not include diastolic pressure in their determinations, the way was not open for them to state approximately the pressure of those beats, and their method of calculating the average amounted to assigning a zero pressure to all the beats which could not be felt at the wrist. This error accounts for the extraordinarily low pressures recorded in some of their cases. The extended "graph" described in Section 3 to represent these beats makes it possible to apply to them the same averaging method as to the waves which can be felt.

The *pulse pressure* so far has not been mentioned. It is clear that its average will be the difference between the average systolic and the average diastolic pressure. Also since waves with highest systolic pressure more often follow the longest pauses (and hence as a rule the lowest diastolic pressures), it is probably true that in cases of auricular fibrillation the greatest pulse pressures are approximately measurable by the difference between the highest systolic pressures and the lowest diastolic. Some light on the variation of pulse pressures below this value might be afforded by a study of the diastolic intervals, but the results would be very problematical, and there appears to be no good way to determine the lower limit of pulse pressure. That the average pulse pressure may have some value is indicated by the results in well marked cases of aortic insufficiency with auricular fibrillation. Figure 8 is from a typical case of this kind. The average pulse pressure is considerably greater than the average diastolic pressure. The usefulness of the average pulse pressure, however, as an index of blood flow, etc., will be limited by the considerations mentioned above in regard to systolic pressure.

SUMMARY

A method is described whereby with the use of the ordinary clinical blood pressure apparatus blood pressure variability may be demonstrated and analyzed. Several types of cardiac arrhythmia are used for illustration. Caution is urged in the interpretation of "average" pressures, especially a distinction should be made between the effective and the abortive beats.

For helpful suggestions I am indebted to Prof. Joseph Erlanger and to my colleague, Dr. James L. Whitney.

CLINICAL STUDIES ON THE RESPIRATION

II THE ACIDOSIS OF CHRONIC NEPHRITIS *

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Since it has been established that under normal conditions the respiratory center is controlled by the reaction of the blood, and that any increase in blood acidity raises the pulmonary ventilation, the clinical conditions associated with acidosis have assumed a new significance. This is especially true of chronic nephritis, a disease in which dyspnea is not infrequently one of the most disturbing symptoms. Lewis and his associates,¹ and Peabody,² have already discussed the association of acidosis and dyspnea in the group of clinical cases which is often classified under the term "cardiorenal disease," but the relation between the two is as yet by no means absolutely clear. In order to get more light on the subject it seemed to be of fundamental importance to obtain rather detailed information as to the mechanism which causes the acidosis, the period at which it begins to develop, the degree to which it attains, and in general the relation which acidosis bears to the clinical course of chronic nephritis.

A considerable body of evidence has already been accumulated to show that acidosis, of a more or less high degree, is apparently a constant accompaniment of uremia. Much, indeed, has been written regarding the possible etiologic relationship between the two conditions. Following the first description of acidosis in uremia by von Jaksch³ who based his work on the titration of blood, there have been published a large number of observations on the carbon dioxide tension of the alveolar air by Straub and Schlager,⁴ Porges and Leimdorfer,⁵ Poulton and Ryffel,⁶ and Peabody,² as well as more limited series of observations on the hydrogen-ion concentration of the blood by Kreiblich,⁷ Rolly⁸ and Peabody.² The result of all these studies has been,

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† From the Medical Clinic of the Peter Bent Brigham Hospital

1 Lewis, Ryffel, Wolf, Cotton and Barcroft. *Heart*, 1913, v, 45, Lewis and Barcroft. *Quart Jour Med*, 1915, viii, 97

2 Peabody, F W. *Studies on Acidosis and Dyspnea in Renal and Cardiac Disease*, *THE ARCHIVES INT MED*, 1914, xiv, 236

3 Von Jaksch. *Ztschr f klin Med*, 1888, xiii, 350

4 Straub and Schlager. *Munchen med Wchnschr*, 1912, lix, 569

5 Porges and Leimdorfer. *Ztschr f klin Med*, 1913, lxxvii, 464

6 Poulton and Ryffel. *Proc Physiol Soc*, June 28, 1913, *Jour Physiol*, 1913, xli, 47

7 Kreiblich. *Wien klin Wchnschr*, 1911, xxiv, 1419

8 Rolly. *Munchen med Wchnschr*, 1912, lix, 1201

in general, to show that uremia, at least in its advanced stages, is very frequently, if not always, associated with an acidosis which is sufficiently marked to alter the normal composition of the blood, and to produce a lowering of the carbon dioxide tension. In cases of chronic nephritis without uremia, on the other hand, these investigations of the blood and alveolar air showed little evidence of an acidosis. The whole subject has been approached from a much more fundamental aspect by Sellards,⁹ and in a most important series of investigations in which the so-called "alkali tolerance" test was used, he not only describes the acidosis of uremia, but demonstrates beyond doubt the fact that acidosis "is present in an appreciable degree in ordinary grades of nephritis." He shows, furthermore, that the acidosis depends on a retention which is due to imperfect excretion by the kidneys, since the extent of acidosis is roughly parallel to the signs of renal suppression. Palmer¹⁰ has also brought forward evidence of the early interference with the excretion of acids in chronic nephritis.

The question of acidosis may be studied from several points of view. Thus, in ordinary clinical work, the examination of the urine is usually regarded as giving all the information that is necessary. Qualitative tests for abnormal acids, such as the acetone bodies, and determinations of the ammonia excretion are the methods most generally in use. The results of these urinary tests are, however, not infrequently far from satisfactory, for they give information only as to the amount of acid that is being excreted by the organism, and leave one wholly in the dark as to the actual conditions existing in the blood and tissues. That the examination of the urine shall have any great diagnostic significance presupposes the fact that the increased acids are being excreted, while it is the failure to excrete acids—whether formed in normal or abnormal amounts—that forms the danger of acidosis. In chronic nephritis, in which interference with the renal function is the most essential element, the usual methods of studying the urine would, of course, be wholly unreliable for giving an index of the formation or retention of acids in the body. Much more significant information can be obtained from the blood. In spite of the large amount of acid that passes into the blood as a result of the ingestion of food and of the processes of metabolism, the normal reaction of the blood remains constant. This preservation of its normal reaction is upheld by the excretion of acids through lungs and kidneys, as well as by the chemical composition of the blood. The latter is peculiarly well adapted to the taking up of a maximum of acid with a minimum change of reaction. When, however, there is a great

9 Sellards Bull. John's Hopkins Hosp., 1912, xxiii, 289, *ibid.*, 1914, xxv, 141

10 Palmer Med. Communicat., Massachusetts Med. Soc., 1913, xxiv, 133

abnormal increase in the formation of acids, or when the acids are not properly excreted by the kidneys, so that large amounts accumulate in the blood, the blood will necessarily become more acid in reaction. Such a rise in acidity will stimulate the respiration, the carbon dioxide tension of the blood will be reduced and the normal reaction of the blood will be maintained. Thus a diminution of the carbon dioxide tension of the blood, or, what is the same thing, a diminution of the carbon dioxide tension of the alveolar air, will be an index of the increase of the nonvolatile acids in the blood. Such an index will be of infinitely greater value as a guide to the condition within the body at any given time than can be obtained from the urine, and is of primary significance when one is considering the subject from the point of view of the control of respiration. Of more fundamental importance would be a means of studying acidosis in the cells or tissues, for it is the preservation of the normal reaction of the cells that is really essential to the organism. Enzyme activities, and in all probability the majority of metabolic processes, proceed best at certain definite reactions, and many can only take place within certain narrow limits of reaction. Unfortunately, methods have not yet been devised which allow us to gain much insight into the obscure field of cellular metabolism, and the problem of tissue acidosis can only be approached indirectly. Probably the most delicate index of acidosis is obtained by the use of the so-called "alkali tolerance" test, first described and studied by Sellards,⁹ but simultaneously worked out by Palmer.¹⁰ In a normal individual the ingestion of 5, or at most 10 grams of sodium bicarbonate suffices to change the reaction of the urine from acid to alkaline, but if there is any acidosis, either from excessive formation or from simple retention of acid, a much larger amount of alkali is required. It seems probable that during the gradual development of an acidosis the organism draws on the reserve supply of base in the tissues to neutralize the acids, and when, subsequently, an excess of base is provided, as by giving sodium bicarbonate, it is used to replenish the exhausted stores in the tissue before it is allowed to pass out in the urine. A comparison of various methods for detecting acidosis shows that the amount of sodium bicarbonate which is needed to change the reaction of the urine is a delicate index of the extent of the acidosis. Moreover, in spite of its simplicity, it gives perhaps the earliest evidence of the development of an acidosis, for it apparently tells when even a small inroad on the reserve supply of bases in the tissues has been made. The "alkali tolerance" test may thus be quite safely considered as a general, rough guide to the degree of acidosis in the tissues. Only at a later period, when a considerable amount of acid has been accumulated in the tissues and in the blood,

does the composition of the blood change so that the alveolar carbon dioxid tension begins to fall. It is of course this latter point—the time at which a shift in hydrogen ion concentration of the blood stimulates the respiratory center and causes an increase of pulmonary ventilation with a consequent lowering of alveolar carbon dioxid tension, that is of special significance from the point of view of studies of the respiration.

In the series of cases of chronic nephritis reported on in the present paper an attempt has been made to correlate what may be considered as two stages in the development of the acidosis, with the course of the disease as indicated by renal function tests. The “alkali tolerance” test has been applied to find the earliest indication of acidosis, and the carbon dioxid tension of the alveolar air has been determined to show when the acidosis has begun to affect the balance between volatile and nonvolatile acids in the blood. The usual method for the “alkali tolerance” test has been to give 5 grams of sodium bicarbonate by mouth every two hours until the urine becomes alkaline to litmus paper. This rather rough method has given results that are in general wholly satisfactory. The high normal limit is taken as 10 grams of sodium bicarbonate. In most normal persons the urine becomes alkaline after 5 grams. The carbon dioxid tension of the alveolar air was determined by the Plesch-Higgins¹¹ method, which has been extensively used in this laboratory, and has proved itself most satisfactory for clinical work. As an indication of the severity of the nephritis the functional capacity of the kidneys was studied by the phenolsulphonephthalein test, and in some instances, by the determination of nitrogen retention. Dr. J. P. O’Hare has been kind enough to give me his figures for the total nonprotein nitrogen, or for the urea nitrogen of the blood in the cases which were studied by him in another connection.

Since cardiac insufficiency may of itself cause an acidosis, it is of importance from the present point of view that the cases of nephritis to be studied should be as free as possible from any involvement of the heart. Ideal cases are, of course, very difficult to find, as so large a proportion of all cases of chronic nephritis are associated with cardiac hypertrophy, and, in the later stages at least, with evidences of cardiac weakness. By careful selection, however, a group of cases has been accumulated in which the cardiac element could be fairly safely ruled out. Many gave in their histories symptoms suggesting myocardial weakness, such as dyspnea on exertion, and others had passed through periods of more or less definite cardiac decompensation, but when they were investigated for the present purpose the cir-

11 Boothby, Walter M., and Peabody, F. W. A Comparison of Methods of Obtaining Alveolar Air, *THE ARCHIVES INT. MED.*, 1914, xiii, 497.

culatory element was absent, or, in a few instances, wholly secondary in importance

The cases fall naturally into three groups. The first (Table 1) consists of patients in whom there was evidence of a definite, but not particularly severe nephritis. The diagnosis was based on the urinary findings and usually on an associated hypertension and cardiac hypertrophy. In all of these cases the phenolsulphonephthalein output, and the determinations of blood urea, with one exception, indicate that the action of the kidneys was functionally sufficient. The alkali tolerance test was normal in every case in which it was tried, and the carbon dioxide content of the alveolar air was found to be normal. Thus, in this series of patients with comparatively mild chronic nephritis, no evidence of acidosis was found.

TABLE 1—CASES SHOWING NORMAL PHTHALEIN OUTPUT AND NORMAL ALVEOLAR CARBON DIOXID TENSION

Case No	Hospital No	Blood Pressure mm Hg	Phthalein Output in Two Hrs Per Cent	Urea Nitrogen in Blood mg	Alkali Tolerance Gm NaHCO ₃	Alveolar Carbon Dioxid Tension mm
1	2552	110	58		10	50.3
2	2324	90	52	9.25	10	42.3
3	2548	140	65	9.4	10	43.5
4	M'D	178	63		10	49.9
5	2077	210	50	22.5	10	43.4
6	17319	220	55		5	
7	428	195	70			44.1
8	2081	160	52			40.0*
9	426	100	55			42.7
10	2237	160	60	12.3	10	

* Cardiorenal compensated

Table 2 consists of a group of rather more severe cases. The phenolsulphonephthalein test and the nitrogen retention determinations show that in all of them the functional capacity of the kidneys was below normal. The degree to which renal efficiency was impaired varied considerably, being slight in some instances, but great in others. The alveolar carbon dioxide determinations were always normal, indicating that there was no great accumulation of nonvolatile acid in the blood. "Alkali tolerance" tests were done in only five cases, but in all of these there was an increase above normal in the amount of sodium bicarbonate required to make the urine alkaline in reaction. One patient became nauseated after taking 50 grams, and it was not possible to complete the test. It is worth noting that the increase in "alkali tolerance" runs exactly parallel to the decrease in phenolsul-

phonephthalein elimination Thus in this group of patients with chronic nephritis of higher grade, and with kidneys which are more or less inefficient functionally, the "alkali tolerance" test shows that there may be a loss of base to the body, an early stage in the develop-

TABLE 2—CASES SHOWING LOW PHTHALEIN OUTPUT AND NORMAL ALVEOLAR CARBON DIOXID TENSION

Case No	Hospital No	Blood Pressure mm Hg	Phthalein Output in Two Hrs Per Cent	Nonprot Nitrogen in Blood mg	Alkali Tolerance Gm NaHCO ₃	Alveolar Carbon Dioxid Tension mm
1	2611	195	23	25 *	25	43.6
2	2429	160	39	18.75 †	15	40.3
3	2124	250	36	33.13 †		45.1
4	621	280	Traces	90		40.3
5	2111	180	10	55.5	50 +	42.8
6	477	200	35			41.4
7	2202	245	18	71.9		41.9
8	762	192	25	50.0		40.2
9	590	145	29			42.7
10	2762	260	28	32.5 *	35	41.6
11	655	230	0	279.0		41.3
12	2739	200	12	42.7 *	20	41.4

* Urea nitrogen

TABLE 3—CASES SHOWING LOW PHTHALEIN OUTPUT AND LOW CARBON DIOXID TENSION

Case No	Hospital No	Blood Pressure mm Hg	Phthalein Output in Two Hrs Per Cent	Nonprot Nitrogen in Blood mg	Alkali Tolerance Gm NaHCO ₃	Alveolar Carbon Dioxid Tension mm
1	2564	240	Trace	101.5 ~	80	31.1
2	2567	195	Trace	57.5 †	55	35.8
3	2006	200	Trace	90.9	50 +	19.1
4	2111	180	6	55.6 †+	50 +	35.8
5	673	205	0	200.0		33.8
6	2108	160	15	55.5	80	33.7
7	573	230	0	90.5		31.7
8	132	170	0			6.0
9	2730	168	27	48.0 ~	50	35.3

* Urea nitrogen

ment of acidosis, but the alveolar air determinations are normal and do not suggest that the nonvolatile acids are increased in the blood

The nine patients in the third group (Table 3) had very advanced chronic nephritis Six of them died within a few days or weeks of

the time when these observations were made, and the three who were discharged from hospital were given a bad prognosis. The phenolsulphonephthalein test, and the nitrogen retention figures both indicate that the functional efficiency of the kidneys was extremely low. Even in the two instances showing an output of 27 and 15 per cent of phenolsulphonephthalein, the high values for the nonprotein nitrogen and for the urea nitrogen in the blood are evidence of severe nephritis. "Alkali tolerance" tests in six cases show a marked acidosis, the figures being on the whole considerably higher than in the previous group of less severe cases. The alveolar carbon dioxide tension was below normal in every case, and in two instances reached extremely low values. There is, however, no strict parallelism between the clinical condition and the fall in carbon dioxide tension, for while the lowest figures occurred during the days just before death, a tension of 33.8 mm was found in one patient who died in uremia within twenty-four hours. In most of these cases the carbon dioxide tension has been low when the patient entered the hospital, but occasionally it has been possible to follow the development of the acidosis in its relation to the course of the disease. Thus in Case 2111 the patient was in fairly good condition when he came into the hospital. The phenolsulphonephthalein output was 10 per cent in two hours, the nonprotein nitrogen in the blood 55.5 mg, and the alveolar carbon dioxide tension was 42.8 mm. Two weeks later his "alkali tolerance" was tested and found to be 50 grams +. One month after admission the clinical picture had changed and the patient was going down hill rapidly. The phenolsulphonephthalein output was 6 per cent and the alveolar carbon dioxide tension was only 35.8 mm. In two days more it had dropped to 33.4 mm, and in five days he died. In this group of patients, then, with very advanced chronic nephritis, and with kidneys whose functional capacity is greatly reduced, there is evidence of a marked acidosis, involving not only a loss of base from the tissues, but the accumulation of considerable amounts of nonvolatile acid in the blood.

The facts which have been brought out here all bear out the theory that the acidosis of renal disease is due to retention. This is in accordance with the views held by Sellards¹² and with the opinions of Porges and Leimdorfer¹³ regarding the cause of the acidosis of uremia. Apparently, so long as the functional capacity of the kidney is unimpaired, or is so slightly decreased that there is no demonstrable retention of phenolsulphonephthalein or of nonprotein nitrogen, there are no signs of acidosis. As soon as there begins to be any retention, it

12 Sellards Bull Johns Hopkins Hosp, 1914, xxv, 141

13 Porges and Leimdorfer Ztschr f klin Med, 1913, lxxvii, 464

is frequently found that an acidosis is developing Sellards¹⁴ says that "in all cases in which the tolerance to bicarbonate is markedly increased, the phenolsulphonephthalein output is very low On the other hand the excretion of bicarbonate is practically normal in some of these cases in which the phenolsulphonephthalein test shows a functional insufficiency "

An interference with the excretion of acids runs roughly parallel to the interference with the excretion of phenolsulphonephthalein, and the retained acids draw on the reserve supply of base in the body These reserves suffice to protect the body from the development of a serious grade of acidosis for a long time, for it is only when excretion is very markedly limited that this protective mechanism fails and acids begin to accumulate in the blood If large amounts of base are supplied to the body, even after a severe acidosis has developed, the alveolar carbon dioxide will rise, and conditions will become normal again It may then be quite a long time before this new reserve is used up and before the carbon dioxide tension begins to fall again The situation is very different in severe diabetic acidosis in which abnormally large amounts of acids are being formed, and correspondingly large amounts of base are required In chronic nephritis the formation of acids is probably not increased, but the body gradually goes into bankruptcy, as they are not excreted, and the organism loses the advantage of the mechanism by which the kidney excretes acid and retains base for further use There is, of course, the possibility that the amount of acid substances formed in chronic nephritis is somewhat more than the normal Mosenthal's work¹⁵ showing a specific increase of protein metabolism, bears on this subject This, however, would not be a large factor, and in general, the acidosis of chronic nephritis may be considered as being due to the retention of the normal acid products of metabolism

Having shown that during the later stages of chronic nephritis a sufficient grade of acidosis may develop to cause a depression of the carbon dioxide tension of the alveolar air, it is now of importance to consider in more detail how great the acidosis actually is, and what relation it bears to uremia In most cases the acidosis does not seem to be particularly great The alveolar carbon dioxide tension usually runs from 25 to 35 mm during the days in which uremia is developing and even after coma has set in The significance of these figures may perhaps be best understood by comparing them with the results found

14 Sellards Bull Johns Hopkins Hosp, 1912, xxiii, 289

15 Mosenthal, H O Nitrogen Metabolism and the Significance of the Non-Protein Nitrogen of the Blood in Experimental Uranium Nephritis, THE ARCHIVES INT MED, 1914, xiv, 844

in diabetes, in which it has been quite definitely established that while a tension of 30 to 20 mm indicates a serious acidosis, the condition is usually not critical until it drops below 20 mm. During diabetic coma the carbon dioxide tension is apt to be about 10 mm or less. This comparison of the alveolar air in diabetes with that in nephritis suggests, of course, that in many cases of uremia acidosis plays a very subordinate part. There is, however, a well-defined group of cases of advanced chronic nephritis in which the whole clinical picture simulates closely that of diabetic acidosis. These patients are at first somnolent, and then pass into a deep sleep or coma. The respiration becomes deeper, and when the case is fully developed, there is typical "air hunger." Acetone and diacetic acid are present in only small amounts in the urine, or they may be absent. In this group of cases the onset of severe, terminal, uremic symptoms is associated with a fall of the carbon dioxide tension to values as low as are found in diabetic coma. In one instance the tension was 4.59 mm during coma. Another was of unusual interest in the response shown to alkali therapy. The patient was a woman, 45 years old, with a history of nephritis extending over several years. Her blood pressure was about 200 mm and the nonprotein nitrogen in her blood had risen to 90 mg per 100 cc of blood. For over a month the phenolsulphone-phthalein test had shown practically no elimination of the dye in her urine. Her general condition, however, remained rather remarkably good, and except for headaches there was no evidence of uremia until January 11. On this day she first began to complain of being short of breath. The alveolar carbon dioxide tension was 19.1 mm. Two days later, on January 13, she was unconscious and her respiration was slow but so deep as to be quite typical of "air hunger." The alveolar air was not taken at this time, but 300 cc of 4.7 per cent sodium bicarbonate solution were given intravenously. On the following morning the carbon dioxide tension was 23.4 mm. This indicated a marked acidosis, and as the "air hunger" persisted, a further intravenous injection of 700 cc was given later in the day. On the following morning the clinical picture had entirely changed. The patient was conscious and recognized every one, but she was greatly nauseated and still looked very sick. The "air hunger" had disappeared and the respiration was of the shallow, slow, and irregular type with rather prolonged periods of apnea such as is commonly seen in advanced nephritis. The alveolar carbon dioxide tension had risen to the normal value of 41.5 mm. On the next morning it had fallen to 36.9 mm. Respiration was slightly deeper, with occasional sighing respirations, but it did not suggest "air hunger." She was conscious and responded fairly well to questions but was very dull. An attempt was

made to ward off the further development of acidosis by giving 375 c c of 5 per cent sodium bicarbonate intravenously, but it was unsuccessful, for on the next day the alveolar carbon dioxide tension had dropped to 25.1 mm, her respiration was deeper and more rapid, and she was becoming unconscious. On January 17 she was comatose, and had begun to have convulsions. Another intravenous alkali injection was without effect and the patient died January 18. Sellards has described similar cases of uremia in which "air hunger" was a prominent symptom, and indeed the clinical picture is one that is generally recognized.

The investigations described here agree well with those of other observers, and make the relation between acidosis and uremia quite clear. It seems certain that some degree of acidosis is present in all cases of uremia. Usually it is marked enough to cause a lowering of the alveolar carbon dioxide tension, but often it is not of high enough grade to be of itself an important element in the symptomatology of the case. In a limited number of cases the onset of severe uremia is associated with the development of an acidosis which is extensive enough to produce coma and "air hunger" and which may dominate the clinical picture.

The therapeutic results obtained by the administration of alkali in uremia confirm this point of view. In the case just described the sodium bicarbonate was undoubtedly beneficial in its action, for it relieved dyspnea and restored consciousness. The improvement was only temporary, however, for acidosis is certainly only one factor in uremia, and the patient was necessarily doomed to succumb to the other results of renal suppression. Similar and even better results are reported by Sellards after the administration of alkali in this type of case. The evidence is thus good that in the group of uremic patients with signs of marked acidosis, alkali therapy is indicated, and may produce great temporary improvement. In the group of cases in which the acidosis only produces a slight fall in the alveolar carbon dioxide tension, and in which there are no symptoms directly due to the acidosis, the results obtained by giving alkali are much more questionable. The fact that the body has lost part of its reserve supply of base, and that it is on the edge of a severe acidosis makes the administration of alkali a logical indication. The effect is hard to determine, as there are so few definite symptoms to go by.

The respiration in advanced cases of chronic nephritis is not typical of acidosis even when there is a slight depression of the carbon dioxide tension. As in diabetes, the evidences of "air hunger" usually begin to appear only when the carbon dioxide tension drops below 20 or at most 25 mm. Most cases of advanced nephritis have an irregular, shallow,

periodic type of respiration, with a tendency to the development of Cheyne-Stokes respiration particularly when they begin to sleep. The irregularity or periodicity of the breathing is frequently not very evident on casual examination, but it comes out as soon as pneumographic tracings are taken. At night, with the general depression of nervous excitability, the periodicity becomes more marked, and in many instances the distressing attacks of nocturnal dyspnea are due to Cheyne-Stokes respiration. Even when the periods of apnea and dyspnea are not definitely demarcated, a pneumographic tracing may show that a period of very shallow breathing, followed by a short interval of apnea, precedes the dyspneic attack which arouses the patient from his sleep to severe physical and mental distress. This periodic type of respiration is not a result of acidosis, for, in a number of cases, pneumographic records have shown that it exists after enough alkali has been given to bring the alveolar air back to its normal value, in exactly the same way that it did before the acidosis was overcome. It was also interesting to notice in the case of nephritis with acidosis described above, that when enough alkali had been given to raise the carbon dioxide tension and overcome the "air hunger," the respiration became shallow and irregular, just as it is in most advanced cases of chronic nephritis. It was thus possible to separate the type of respiration characteristic of nephritis itself from that which depended on the acidosis occurring during the nephritis. On the other hand, some patients with milder acidosis seem to be distinctly more comfortable and to have much better nights after they have received alkali. Inasmuch as patients with acidosis are rendered dyspneic more easily than are normal persons by the inspiration of carbon dioxide,¹⁶ and are thus apparently peculiarly susceptible to dyspnea, it would seem wholly likely that overcoming the acidosis in patients with advanced nephritis might increase their comfort by diminishing the tendency to dyspnea.

When chronic nephritis is associated with cardiac weakness the question of acidosis becomes much more complicated, as a new element is added. There is not only the acidosis of nephritis, due to inefficient renal excretion, but there may also be an accumulation of acid metabolic products which are the result of an inadequacy of the supply of oxygen reaching the tissues. Such patients may show a lowering of the alveolar carbon dioxide tension when they are first seen, and while their hearts are more or less decompensated. If, however, the kidneys are not too badly involved, the acidosis will disappear shortly. As the circulation becomes compensated, the production of acids due to circulatory insufficiency will cease, oxidations will go on normally, and the kidneys will excrete the accumulated acids. Since the reserve supply

16 Peabody THE ARCHIVES INT MED, this issue, p 955

of base may be decreased in patients with chronic nephritis, so that they are constantly nearer than normal to the development of an acidosis, it is quite probable that a degree of cardiac insufficiency which will produce dyspnea in them would not affect a person who could neutralize and excrete acids normally

CONCLUSIONS

In mild cases of uncomplicated chronic nephritis, in which the phenolsulphonephthalein test shows a normal renal function, there is usually little or no acidosis

More advanced cases, showing moderate or even extreme decrease in the phenolsulphonephthalein output, show an acidosis by the "alkali tolerance" test, but there may be no fall in the alveolar carbon dioxide tension

Only in very advanced cases is the acidosis usually so marked as to cause a decrease in the alveolar carbon dioxide tension. Most cases in which the alveolar carbon dioxide tension is below normal show a phenolsulphonephthalein output which is below 10 per cent in two hours. On the other hand cases showing a phenolsulphonephthalein output of "traces" or less may have a normal alveolar carbon dioxide tension

The acidosis of chronic nephritis is due to a retention, resulting from inefficient renal excretion

Acidosis is probably a very constant feature of uremia, but only in a limited number of cases is it of sufficient grade to cause definite clinical symptoms analogous to those seen in advanced diabetes. In these cases the symptoms caused by the acidosis may be relieved by alkali therapy

THE ACTION OF THE VAGI ON THE HEART IN PAROXYSMAL TACHYCARDIA

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The influence of the vagi on the heart in paroxysmal tachycardia is of interest because of the possible causative rôle derangements of the nervous mechanism controlling heart rate may play in the disease, and because vagus stimulation may in some cases bring about a cessation of the tachycardia. I wish to consider this influence from a somewhat different point of view, as it seems possible to draw certain inferences concerning the mode of action of the vagi, by comparing cases in which vagus stimulation by pressure is effectual in stopping the tachycardia with those in which it is ineffectual.

Cohn and Fraser¹ have reported two cases of paroxysmal tachycardia which could be stopped by pressure over the vagi, one case apparently of auricular origin in which the right vagus was especially effectual, and the other apparently of ventricular origin in which the left vagus was more effectual than the right. There have been numerous reports of such cases in the literature.

Much less has been written, however, concerning cases in which pressure over the vagi failed to affect the very rapid heart rate, and this failure has apparently not been discussed. I wish to report observations on two cases of paroxysmal tachycardia in which the rapid heart rate could not be influenced by vagus pressure, and to draw some inferences regarding vagus action from a comparison of these two groups of cases.

CASE 1—A young man of 26 walked into the dispensary complaining of heart trouble, which he said came on suddenly. He had been having such attacks for the past five years, lasting from a few minutes to thirty-six hours. There was no previous illness that could be considered as an etiologic factor of a cardiac disorder. His heart was beating at the rate of 204 per minute.

Electrocardiograms were made immediately and numerous attempts were made to affect the heart rate by pressure over one or the other vagus. Electrocardiograms during the paroxysms were not of unusual form (Fig 1).

Pressure over the right vagus was always entirely without effect, the records made during the pressure showing no alteration in rate, form or in relation of auricles to ventricles. On several occasions, however, the left vagus caused cessation of the rapid rate momentarily, but it was resumed, even while pres-

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1 Cohn and Fraser. Heart, 1914, v, 93

sure on the vagus was being maintained (Fig 2) The electrocardiograms obtained during the left vagus pressure showed that, according to the interpretation of the curves, there was a marked lengthening of conduction from auricles to ventricles and finally a block, followed by stoppage of the auricles. The rapid rate was resumed at first by contractions of ventricular origin or by ventricular asynchronism following auricular contractions. The action of the left vagus, when effectual, was quite constant (Fig 3) The paroxysm ceased suddenly about ten hours later, when the patient was in the hospital, and electrocardiograms of the normal, slow rate were obtained (Fig 4) They do not differ materially, when the change of rate and consequent spreading out of the various waves is considered, from those obtained during the tachycardia.

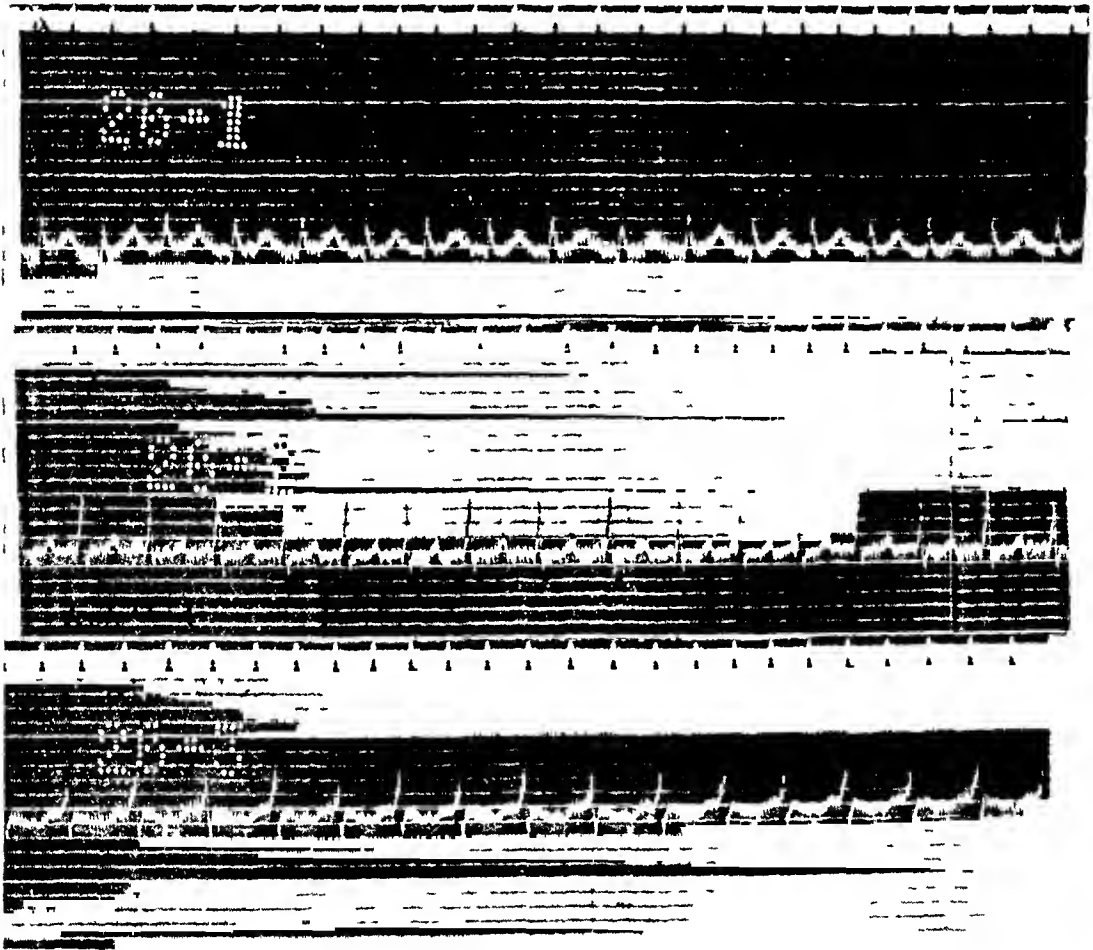


Fig 1 (Case 1) —Record obtained during an attack of tachycardia

During the normal slow rate, vagus pressure over either nerve was definitely effectual in slowing the heart, the right being more effectual than the left. When 1/50 grain of atropin was administered hypodermically, the heart rate as recorded by electrocardiograms showed an increase of twenty-seven beats per minute as is shown by the accompanying chart (Fig 5). The patient left the hospital, having had no further attacks of tachycardia while under observation, but has had frequent attacks during the past year, as reported by his physician.

CASE 2—A woman of 39 who had had rheumatism at the age of 10 and again at 27, gave a history of attacks of cardiac palpitation and rapid heart action beginning at the age of 15. These attacks have been more frequent

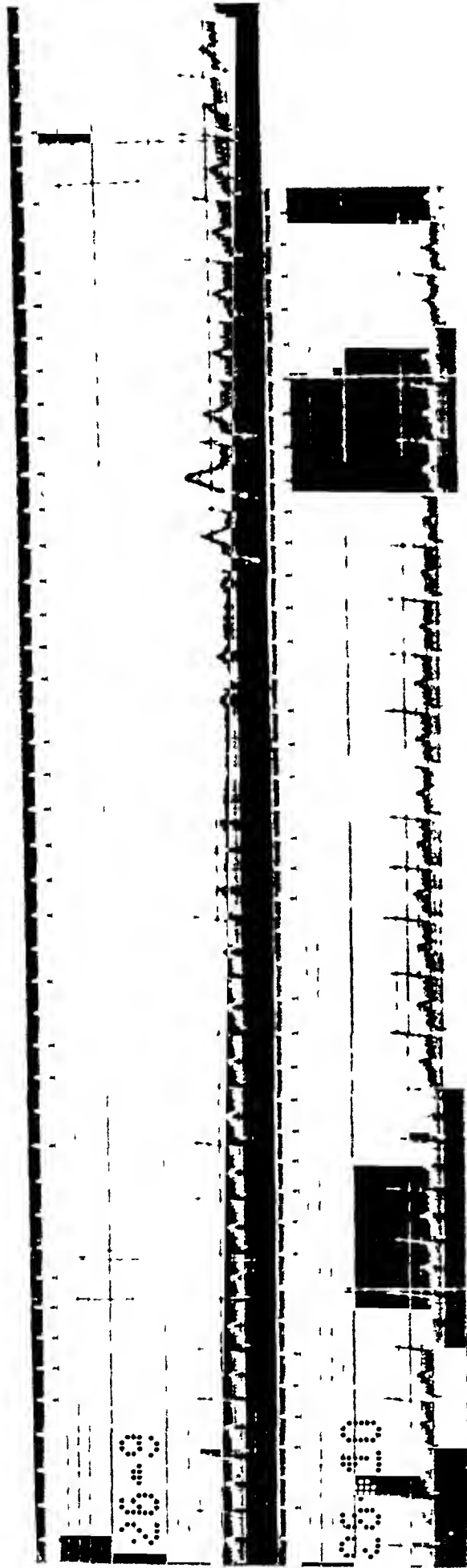


Fig 2 (Case 1) —Record obtained while pressure over each vagus was being excited. Momentary effect of left vagus pressure and absence of effect of right vagus pressure are seen

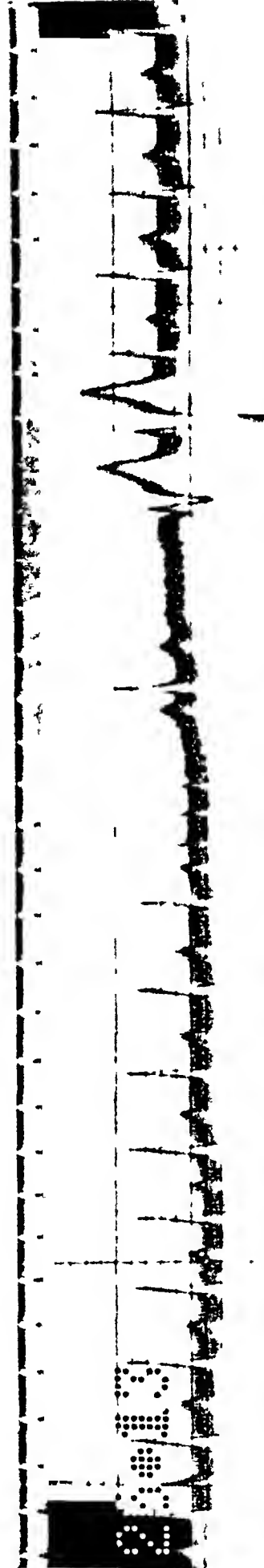


Fig 3 (Case 1) —Record obtained during left vagus pressure, showing the constancy in the response to pressure over this nerve

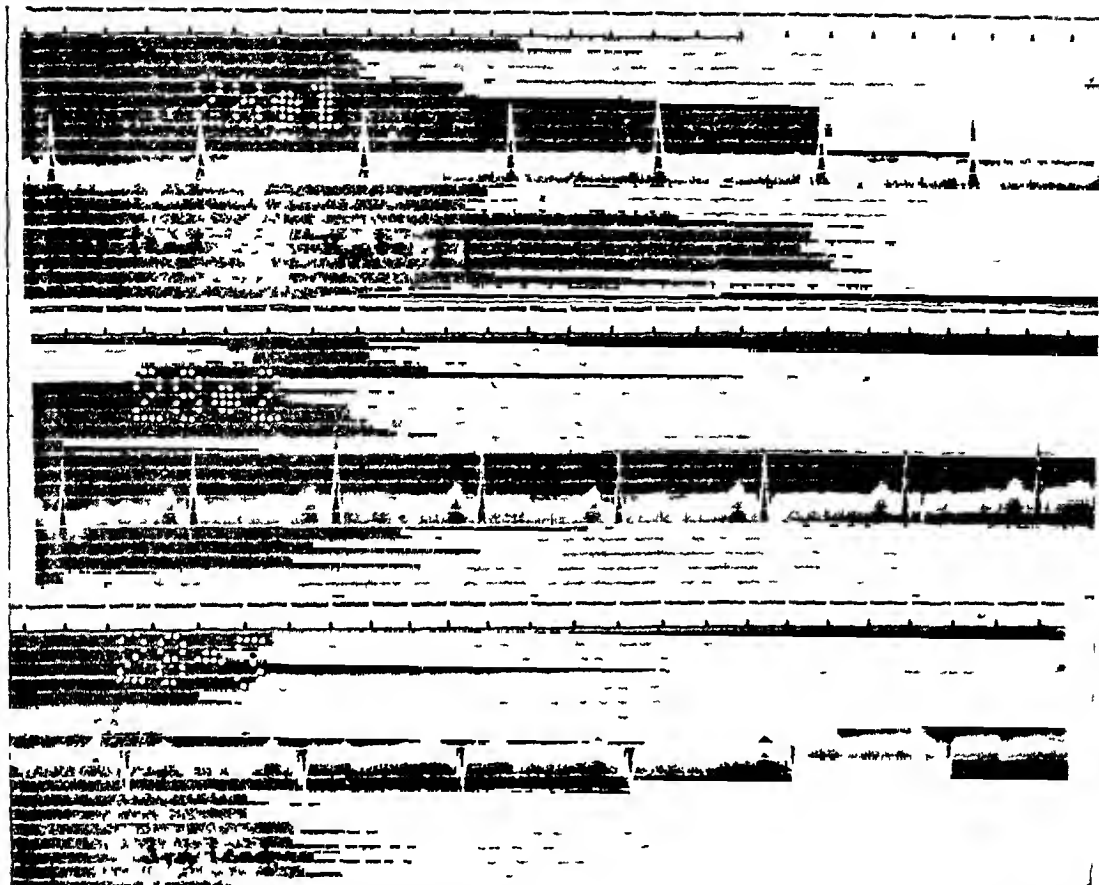


Fig 4 (Case 1) —Record obtained after the heart had resumed its normal rate

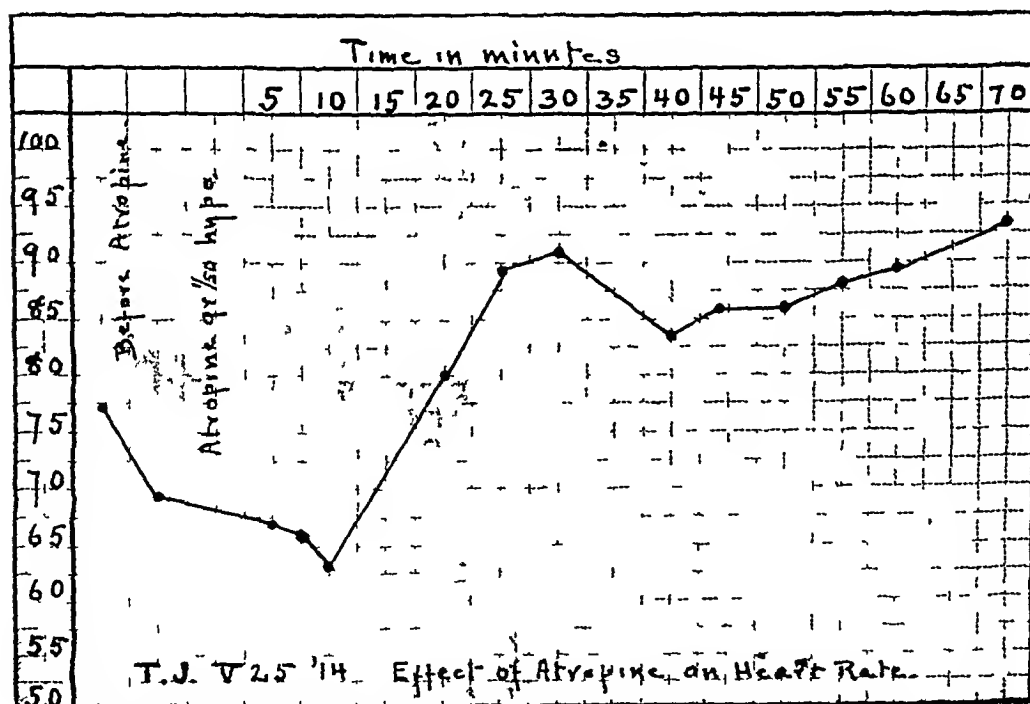


Fig 5 (Case 1) —Chart showing the increase in the heart rate following the administration of atropin

during the past year, but have not materially interfered with her duties as trained nurse doing institutional work. The attacks begin and end suddenly, and last from about one hour to three days. They can be stopped at times by vomiting and the patient sometimes takes an emetic to produce this result. She has aortic and mitral regurgitation. During her stay of several weeks in the hospital she had one attack lasting about two hours, when her heart rate was 220. Electrocardiograms were obtained during this attack (Fig 6). During this attack pressure on each vagus was made several times and the records

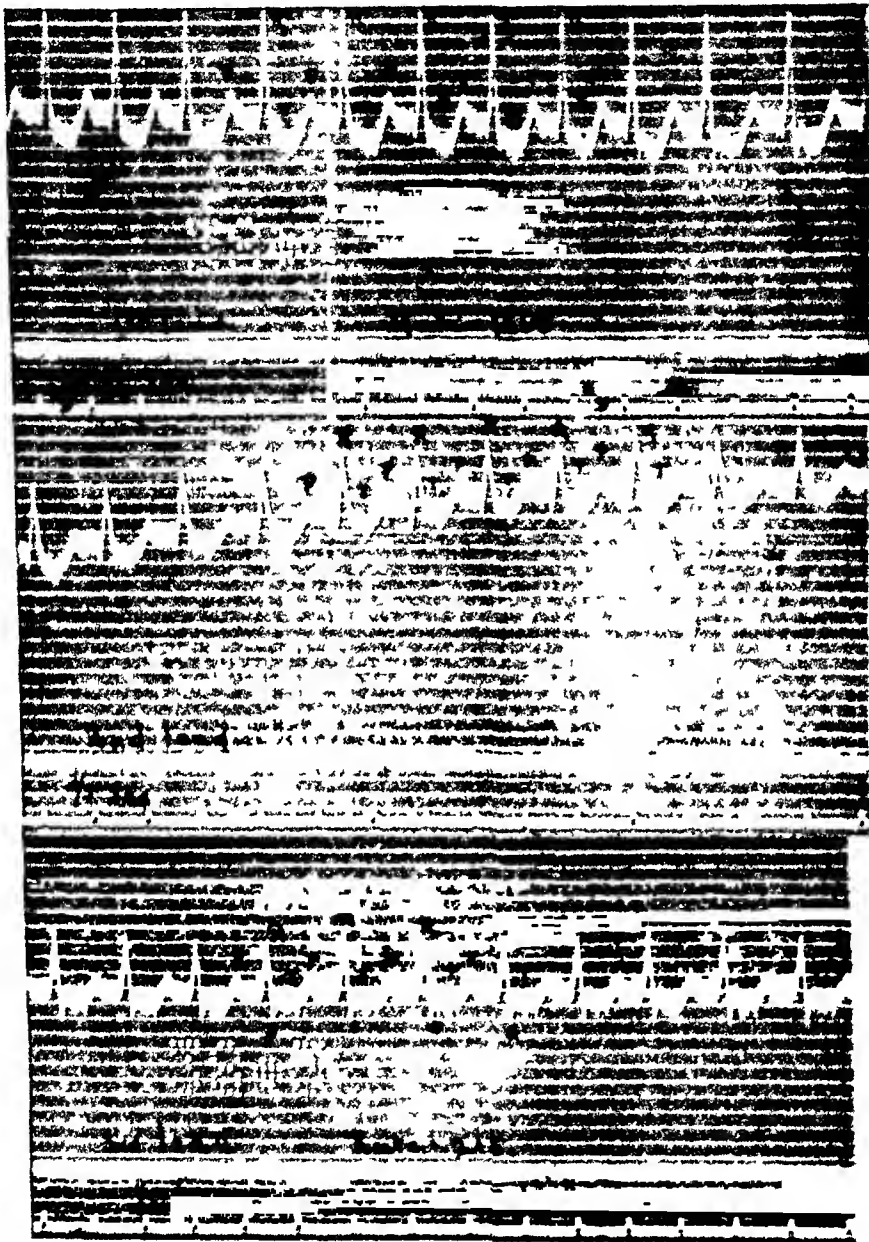


Fig 6 (Case 2) —Record obtained during an attack of tachycardia

made during this procedure showed that the rate and cardiac mechanism were entirely unaffected. The tachycardia ceased spontaneously.

The curves obtained during the time of normal slow cardiac activity showed a definite change in form of the complexes (Fig 7) with a very distinct splitting of the P wave in the second lead, and the frequent occurrence of premature ectopic auricular contractions. Pressure over each vagus was effectual in causing a slight slowing of the cardiac rate and the hypodermic injection of 1/30 grain of atropin caused an acceleration of about thirty beats per minute, as is shown in the chart (Fig 8). It did not produce tachycardia.

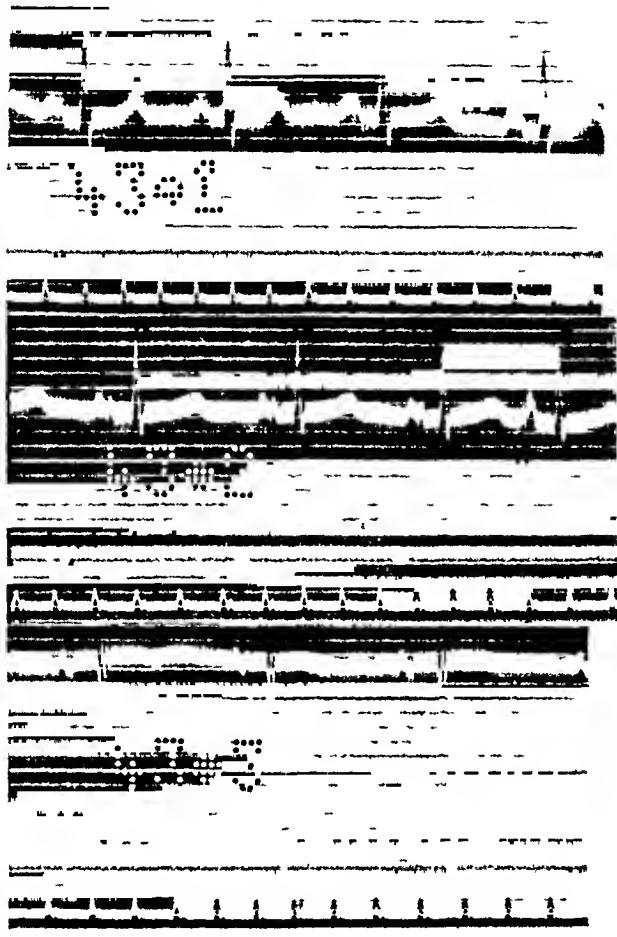


Fig 7 (Case 2) —Record obtained after the heart had resumed its normal rate

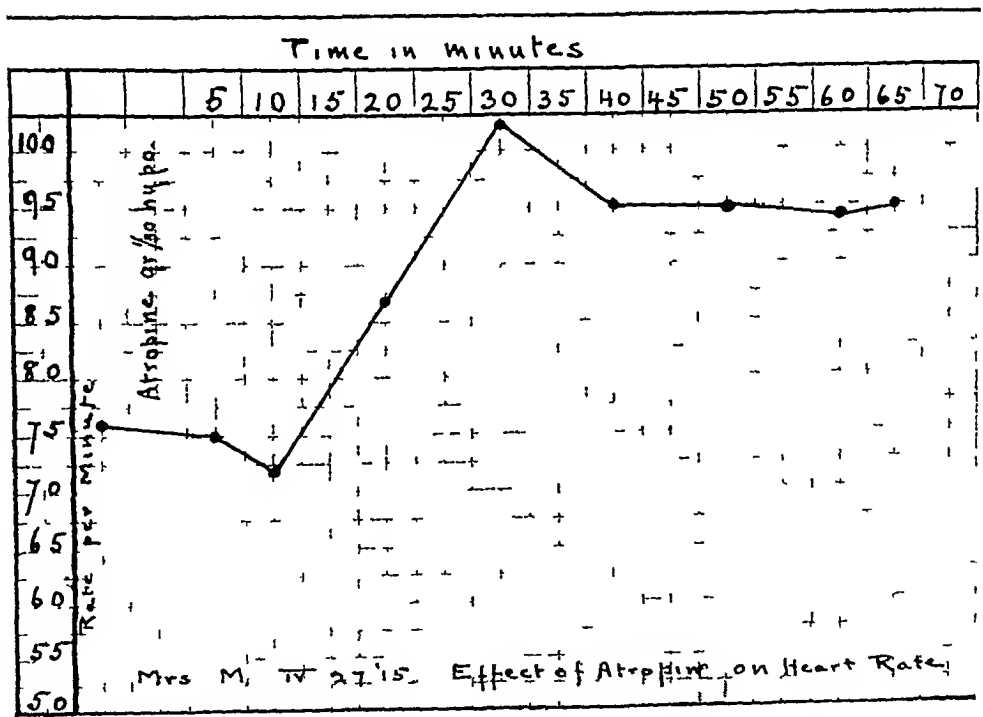


Fig 8 (Case 2) —Chart showing the effect of atropin on heart rate

These two cases of paroxysmal tachycardia are representative of those in which vagus pressure fails to abolish the tachycardia. The cause of the ineffectiveness is not, however, any permanent derangement of the cardiovagal inhibitory mechanism as in both cases the heart rate was slowed by vagus pressure and increased by vagus paralysis with atropin. Why is it then that stimulation of the vagi by pressure is effectual in some cases and not in others? It seems probable that this difference depends on the character of the cardiac derangement responsible for the tachycardia. It is generally held that true paroxysmal tachycardia usually depends on rapid stimulus

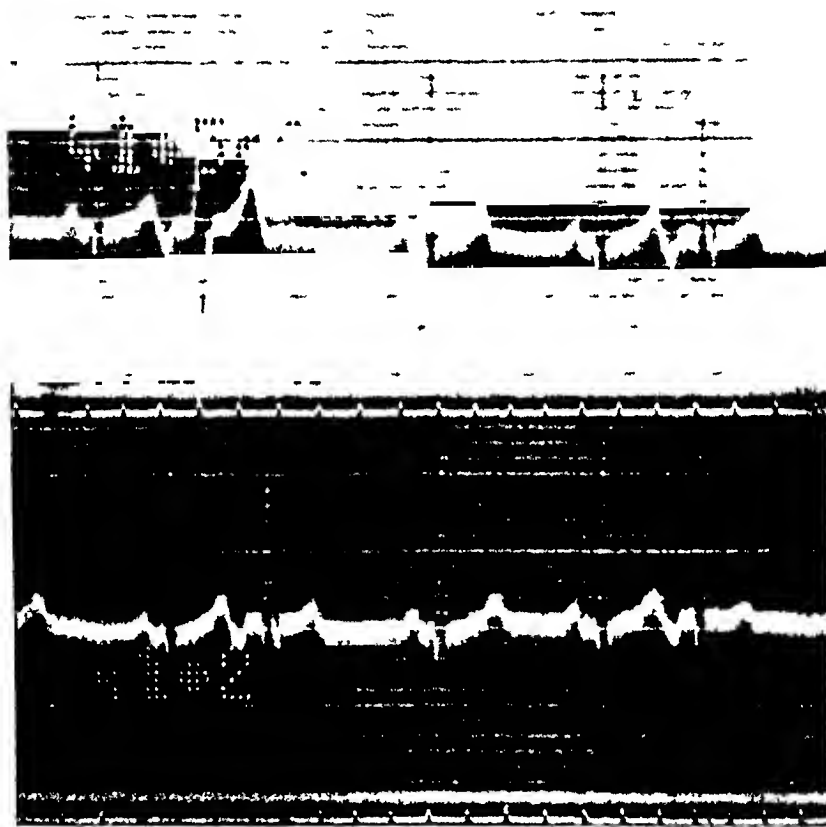


Fig 9—Record showing variations in the form of the ventricular complexes which may follow ectopic auricular contractions

formation in a point outside of the site of the normal cardiac pacemaker, and that it consists of rapidly recurring ectopic beats. These ectopic beats usually arise in a given case in the same part of the cardiac structure. It seems probable that the influence which the vagi will have in controlling these ectopic beats depends on the anatomical relation between the distribution of the vagi and the point taking up the rôle of hyperactive pacemaker. In some cases this point may lie in a part of the heart to which the right vagus is especially distributed, as in Cohn and Fraser's first case, in others, this point may lie in a zone to which the left vagus is more completely distributed, as

in their second case. Other cases may owe their tachycardia to a point of origin to which one nerve only is distributed, but so meagerly as to have slight control over it, as in our first case, while the seat of origin in others may lie in a point of the heart to which the vagus has no distribution and therefore cannot influence it, as in our second case. These cases are brought forward as further evidence for the idea that the influence of each vagus on the heart depends on its anatomical distribution, as has been already suggested,² in accounting for the differences in the effects of the right and left vagi.

It is not permissible, however, to use these cases as evidence of the exact distribution of the vagi, as it seems impossible to locate the point of origin of the abnormal stimuli from the form of the electrocardiographic curves. Curves obtained from a case with ectopic premature auricular contractions, have shown that these abnormal contractions, although suprajunctional in origin, as attested by a conduction time of normal or slightly prolonged length, may give rise to ventricular complexes of various and abnormal forms (Fig 9). In paroxysmal tachycardia, when the ventricular complex is quite similar to that obtained when the heart is beating at a normal slow rate, the point of origin is surely not in the ventricles, but an abnormal form of ventricular complex obtained during the tachycardia should not, in the light of the curve shown in Figure 9, be considered as conclusive evidence of a ventricular origin of the tachycardia.

These cases of tachycardia may be taken, therefore, only as evidence that the influence of the vagi differs in degree on different parts of the heart, and that this difference probably depends on their anatomical distribution.

2 Robinson and Draper Jour Exper Med, 1912, xv, 14

THE CARBOHYDRATE METABOLISM IN HYPERTHYROIDISM AS DETERMINED BY EXAMINATION OF BLOOD AND URINE *

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A lowered tolerance to carbohydrate, as shown by alimentary and spontaneous glucosuria, has long been a well-recognized symptom of hyperthyroidism, and by many authors regarded as a most important one. Scarcely any two observers agree, however, as to the frequency of its occurrence, and many hypotheses have been advanced to explain its presence in some cases and absence in others.

It was thought that a systematic study of the sugar in the blood concomitantly with that of the urine under uniform conditions might throw some light on this subject, and give us a more accurate knowledge of the frequency and degree of lowered carbohydrate tolerance in this disease. For this reason the present work was undertaken. While it was in progress, Flesch¹ reported a series of forty cases of hyperthyroidism with special reference to the concentration of sugar in the blood under various conditions. His results, which are at variance with mine, are here briefly outlined.

1 No case showed spontaneous hyperglycemia. Only nine cases, six before and three after operation, however, were studied fasting, and of these, one before operation gave a blood-sugar reading of 0.102 per cent, and one of the three examined after operation showed 0.110 per cent.

2 Sixty per cent of the cases showed an "alimentary hyperglycemia," blood being taken one hour after 100 gm of glucose.

In view of what is to follow, it seems desirable to point out that Flesch worked with the old Knapp method as used by Tachau, with 15 cc of blood. This method is little used now, because of its unwieldiness and lengthy technic.

Flesch did not examine the urine for sugar in any of his cases.

Tachau² found an alimentary hyperglycemia in a few cases of hyperthyroidism, and failed to find it in others.

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* From the Blumenthal Fellowship Foundation of the Medical Clinic, Presbyterian Hospital, Columbia University.

1 Flesch, Max. Beitr. z. klin. Chir. (Bruns'), 1912, p. 236.

2 Tachau. Deutsch. Arch. f. klin. Med., 1911, civ, 445.

These observations, outside of a few isolated cases, reported by other observers, are the only ones to date. All lack uniformity in method of estimating blood sugar, condition of patient at time of taking blood, as regards diet, fever, etc., and in their failure to compare normal controls with the cases studied.

A review of the literature on glucosuria in hyperthyroidism is to be found in Rosenberger,³ Allen⁴ or Magnus-Levy,⁵ and Schulze.⁶

Its frequency, either spontaneous or alimentary, is, as I have said, much disputed, the highest figures giving 69 per cent and the lowest less than 1 per cent. Garrod, in his Lettsonian Lectures⁷ sums up as follows: "Undoubtedly in many cases no diminution of tolerance can be detected, but my own experience leads me to take my stand with those who hold that it is by no means an uncommon phenomenon. In not a few cases, spontaneous excretion of sugar, of a transitory or intermittent kind, is observed, if carefully watched for, and in others, as I have already mentioned, persistent glucosuria with the usual attendant symptoms which go to make up the picture of diabetes." And later he adds, "In the cases in which transitory spontaneous glucosuria occurs, the output of sugar tends to be small, under 1 per cent; it may be present on a single day only or on several successive days, or it may recur at intervals." This is also in accord with H. Straus.⁸

The results of the present study lead to the same conclusion, and it is very probable that the failure to find glucosuria has been due to lack of care in searching for it, and also the failure to search daily over long intervals.

METHOD OF STUDYING CASES, AND TECHNIC

In all, twenty-seven cases of hyperthyroidism were studied. These varied from very severe to extremely mild ones, but all had sufficient symptoms or history or both to warrant the diagnosis.

To control these observations, twenty-five other individuals have been studied. These include healthy adults and patients convalescing from various diseases. Each case has had at least one blood-sugar determination and some have had many. Blood was always taken at a fixed time after breakfast, in most instances three hours and in some cases two and a half hours. In several cases the blood sugar was also estimated before breakfast when the stomach was empty.

3 Rosenberger, Franz. *Die Ursachen der Glykurie, ihre Verhütung und Behandlung*, München: Müller, 1911.

4 Allen, F. M. *Studies Concerning Glucosuria and Diabetes*. Boston, Leonard, 1913, p. 144.

5 Magnus-Levy in von Noorden. *Metabolism and Practical Medicine* III, 983.

6 Schulze, Fritz. *Beitr. z. klin. Chir. (Bruns')*, 1912, p. 207.

7 Garrod. *Lancet*, London, 1912, i, 629.

8 Straus, H. *Deutsch. med. Wchnschr.* 1897, XXXIII, 309.

Jacobsen has shown that in normal individuals, after feeding 100 gm of glucose or 100 gm of starch in the form of bread, there is a rise in the blood sugar as compared with the preformed values. This rise occurs often in the first five minutes, reaches its height in half an hour, and then gradually returns to the level of the preformed value and often lower. On an average, this occurred in two hours, sometimes in three quarters of an hour, and in one case not until three and a half hours after.

Tachau⁹ claims a return to fasting blood-sugar level as early as one hour after the administration of 100 gm of glucose, but he contrasts fasting values with the values of other normal individuals observed one hour after 100 gm of glucose.

The evidence so far certainly points to the fact that in normal individuals and in convalescents in whom there is no reason to suspect derangement in carbohydrate metabolism, the blood sugar, after an ordinary hospital breakfast averaging 75 gm of carbohydrate with protein and fat, will return to the fasting level in less than three hours, and in most cases in less than two hours. The same holds true for the administration of 100 gm of glucose when given fasting. There are exceptions to this, but they are few, as Table 1 will show.

All blood-sugar determinations in this table, as in the following table, were made with from 10 to 20 c c of blood. In nearly all instances, duplicate samples of blood were employed as a control on the technic. The method of removing coagulable protein from the blood was that of Rona and Michaelis, while the sugar was estimated in the filtrate by the Bertrand method, this is probably the most accurate method known for the estimation of the reducing substances in the blood. Glucose was given, when not otherwise indicated, fasting, in lemon juice, 10 c c, and water up to 150 c c.

The patients' urine was examined for the appearance of spontaneous glucosuria in twenty-four hour specimens, and after administration of glucose, at two-hour intervals as indicated in the table.

Fehling's reaction and fermentation were used in the qualitative tests for sugar in the urine, but no tests are reported positive unless they also showed glucozazone crystals. A word with regard to the Fehling reaction. I have tried many of the qualitative tests for sugar, but have found none so satisfactory as the Fehling when done carefully and accurately with quantitative pipets and freshly prepared solutions.

In Table 1, the first ten subjects are all men leading a life of moderate physical activity. Cases 1, 2, 3 and 4 were studied from

⁹ Tachau. *Deutsch Arch f klin Med*, 1911, civ, 437.

TABLE 1—BLOOD-SUGAR DETERMINATIONS IN TWENTY-FIVE CONTROL CASES

Case	Name	Sex	Age	Date	Diagnosis	Blood Sugar Percentage						Urine at 2 hr Intervals Post 100 gm Glucose Specimens	Daily 24 Hr Urine
						Fasting	1 Hr p c *	2 Hrs p c	2 1/2 Hrs p c	3 Hrs p c	2 Hrs Post 100 gm Glucose		
1	M S	♂	27	7/29/14 7/31/14	Normal					082	089	10 12, 12 2 = no sugar	Sugar free (3 days)
2	H A R	♂	28	7/29/14 7/31/14	Normal			057			092	8 10, 10 12, 12 2 = no sugar	Sugar free (2 days)
3	H R G	♂	31	8/10/14 8/12/14 4/ 6/15	Normal			075		087	081	8 10, 10 12, 12 2 = no sugar	Sugar free (3 days)
4	G M	♂	28	8/10/14 8/11/14 9/25/14	Normal				084 087		088		Sugar free (2 days)
5	A B C	♂	29	4/ 7/15	Normal	095							Sugar free (2 days)
6	J P	♂	27	3/31/15	Normal	086							Sugar free (2 days)
7	H V	♂	27	3/31/15	Normal	083							Sugar free (4 days)
8	H L	♂	27	4/ 7/15	Normal	094							
9	H S	♂	27	4/ 9/15	Normal	086							
10	W T L	♂	37	4/23/15	Normal	077							
11	E M	♀	29	4/18/15	Hyperchlorhydria	088	096			081		9 11, 11-1, 1 3 = no sugar, post hospital breakfast	Sugar free (11 days)
12	A F	♀	53	4/28/15	Sclerotic and on stipitation	079	118			094		8-10, 10-12 = no sugar, post hospital breakfast	Sugar free (3 days)
13	L B	♀	18	4/30/15	Cardiac (conv)	086				088		100 gm glucose and breakfast 8-10, 10-12, 12 2 = no sugar	Sugar free (3 days)

* Post cibum (after eating)

14	M M	♂	38	5/ 7/15	Pneumonia (conv)	072	082	.	07	.	9 11, 11-1, 13 = no sugar, post hospital breakfast	Sugar free (2 days)
15	R W	♂	28	12/11/13 12/13/13	Multiple neuritis			086		071	7 9, 9 11, 11 1 = no sugar	Sugar free (3 days)
16	T G	♂	47	12/19/13 12/24/13	Chr arthritis knee				085	.	7 9, 9 11, 11 1 = no sugar	Sugar free (4 days)
17	S E	♀	26	3/ 5/13 3/ 8/13	Conv rheuma tism	.	..		082	000	7 9, 9 11, 11 1 = no sugar	Sugar free (6 days)
18	L A B	♂	33	3/19/13 3/20/13	Cholelithiasis Convalescent		.		087	077	7 9, 9 11, 11 1 = no sugar	Sugar free (3 days)
19	G T	♂	40	1/15/14 1/17/14	Bronchopneu monia (conv)			072		139	7 9, 9 11 = no sugar	Sugar free (4 days)
20	A S	♀	27	4/ 3/13 4/ 5/13	Conv tonsillitis				073	055	7 9, 9 11, 11-1 = no sugar	Sugar free (3 days)
21	B M	♂	25	2/26/14 3/ 5/14	Paroxysmal tachycardia Convalescent	004				091	8-10, 10 12, 12 2, 2 4 = no sugar	Nine exams, no sug
22	N K	♀	50	6/24/13 6/27/13	Retroversion uterus, neuras thenia			097		094	7 9, 9 11, 11 1 = no sugar	Sugar free (4 days)
23	R B	♀	23	5/11/14 5/ 9/14	Nephroptosis, neurasthenia			091		123†	8 10 = sug t +, 10 12 = sug t +, 12 2 = sug ft tr	Twelve exams, su gar 3 times
24	A O	♂	34	2/12/14 2/13/14	Paroxysmal tachycardia			092		093	7 9 = sug ft tr 9 11 = no sugar, 11 1 = no sug tr	Two exams, sugar ft tr once
25	E M	♀	21	7/22/14 7/24/14	Gastroptosis				083	115	7 9 = sug ft tr, 9 11, 11 1 = no sugar	Sugar free (4 days)

† 1 hr p 100 gm glucose

two to three hours after a meal (breakfast), and two hours after 100 gm of glucose given fasting. In none of these cases was there a hyperglycemia or any sugar found in the urine. In one case (Case 2) there was a very low blood-sugar reading obtained two hours after breakfast, while that obtained two hours after 100 gm of glucose was almost twice as high, and yet there was no sugar in the urine, at this time or at any other time.

In the next six cases (Cases 5, 6, 7, 8, 9 and 10), the determinations were made fasting only, and the average reading was 0.087 per cent, while the extremes were from 0.077 per cent to 0.095 per cent. These cases were studied simply to confirm the observations of others, that the blood-sugar level of normal persons was approximately the same from two and a half to three hours after a meal as on a fasting stomach. The average of the first four cases taken after a meal was 0.079 per cent, and if Case 2 be excluded, 0.082 per cent. As will be seen, the average reading from two to three hours after a meal is lower than fasting.

The following four cases (Cases 11, 12, 13 and 14) were studied with a view to determining the blood-sugar curve, beginning before a meal (breakfast) and extending over a three hour period. One person (Case 13) was given 100 gm of glucose with breakfast. All of these patients were ambulant convalescents and clinically cured. None of them had, even during the first part of their stay in the hospital, been very ill and there was no reason to suspect any lowering or increase in their carbohydrate tolerance. The fasting blood sugar averages about the same, 0.082 per cent, as in the normal cases. An alimentary rise is seen in three cases one hour after breakfast, which returns to normal or below, three hours after the meal. Case 12, though showing a higher blood sugar than before breakfast, is still well within normal limits. None showed an alimentary or spontaneous glucosuria.

The next eight cases in this table are for the most part convalescent patients, in whom there was no reason to suspect a lowered carbohydrate tolerance. Cases 15, 16, 17, 18, 19, 20, 21 and 22 all showed from two and a half to three hours after breakfast and two hours after 100 gm of glucose, blood-sugar readings which are approximately the same as in the strictly normal cases and well within normal limits. Case 19 is the only exception, here we have a very distinct hyperglycemia two hours after 100 gm of glucose. There was no sugar in the urine collected over the test period, nor on four other examinations. The patient left the hospital the day following the last examination, and there was no opportunity for further study.

The last three cases given in this table are of separate and individual interest, as their study brought out some results which are analogous to those found in hyperthyroidism.

Case 23, particularly, showed a lowered tolerance to glucose, and brings up the question as to whether there was not some involvement of the suprarenals, the constant stimulation of which, owing perhaps to the nephroptosis, caused a lowered tolerance to carbohydrates. Certainly we cannot consider this a normal case, either clinically or from the standpoint of carbohydrate tolerance, and the well-known lowering of carbohydrate tolerance in pathologic conditions of certain of the endocrine glands is very suggestive.

In Case 24, although there was no actual hyperglycemia there was a definite lowering of carbohydrate tolerance as expressed by the glucosuria, and a possible hyperpermeability of the kidneys to sugar was suggested, but further study in this case was not possible.

In Case 25 the very slightly lowered tolerance to glucose is not explained. The patient was very nervous and poorly nourished.

A summary of Table 1 brings out the fact that in none of the cases, excluding, of course, the last three, was there any glucosuria, either spontaneous or alimentary. This is not in accord with Jacobsen's fifteen "normal cases," eight of whom showed an alimentary glucosuria after 100 gm of glucose. The reason for this discrepancy is not entirely clear, unless it be the fact that in all his "normal cases," glucose was given, from two to four and a half hours after a meal and not fasting, and also that he includes cases among his "normals," whose blood-sugar readings vary from 0.083 per cent to 0.128 per cent, as many as seven of the eight being 0.1 per cent or over before 100 gm of glucose were given. But as the Bang method, by which he estimates sugar, gives uniformly higher results than the Bertrand, comparison with my figures is not possible.

In Table 2 are given twenty-seven cases of hyperthyroidism. The first twenty range from cases of moderate severity to very severe ones, while the last seven in the table were very mild, and in one case, A. P. (Case 24), there was some doubt as to the diagnosis. A majority of the symptoms, however, pointed to hyperthyroidism. The remaining seven cases gave very definite histories of this disease, but most of the symptoms were much diminished or absent at the time of examination. They are given here to emphasize the point that lowered tolerance to carbohydrates may, with other symptoms of this disease, be considerably diminished or disappear entirely, over long periods of time.

From the results given in Table 1, it is clear that with the methods used, over 0.1 per cent of blood sugar is to be regarded as hyperglycemia, provided, of course, that the blood is taken fasting or from two and a half to three hours after breakfast. The cases in which readings over this percentage are consistently seen have given either

TABLE 2—BLOOD-SUGAR DETERMINATIONS IN TWENTY-SEVEN CASES OF HYPERTHYROIDISM

Case	Name	Sex	Age	Date	Blood Sugar Percentage					Urine at 2-hr Intervals Post 100 gm Glucose, Three Specimens	Daily 24 Hr Urine and Comments
					Fasting	1 Hr p c	2½ Hrs p c	3 Hrs p c	2 Hr Post 100 gm Glucose		
1	D M	♀	32	1/27/13 2/7/13 2/10/13			112		120	79 = sugar 0.8%, 9 11 = sugar 0.3%, 11-1 = sugar 0.3% 79 = sugar tr, 9 11 = sugar tr, 11 1 = sugar tr	Sugar tr to ft tr 4 times in 29 exams
2	H R	♀	34	2/28/13 3/3/13 3/24/13 3/25/13				132 117	150 128	79 = sugar 0.6%, 9 11 = sugar 0.3%, 11 1 = sugar 0 79 = sugar ft tr, 9 11 = sugar ft tr, 11 1 = sug 0, 13 = sug 0 79 = sug tr, 9 11 = sug 0	13 exams sugar 3 times (ft tr)
3	R R	♀	40	4/7/13 4/16/13 5/12/13				106 126	112	--	29 exams sugar tr 8 times Febrile (pulm tbc)
4	A G	♀	26	4/22/13 5/1/13 5/8/13				104 120	125	79 = sug +, 9 11 = sug +, 11 1 = sug 0	23 exams ft tr sugar 7 times
5	A M	♀	22	5/22/13 5/26/13 6/3/13 6/5/13			097	104 091	117	79 = sug 0, 9 11 = sug 0	18 exams sugar once (ft tr)
6	R B	♀	30	10/28/13 10/29/13 11/6/13 12/5/13			108	086 112	207	79 = sug ++, 9 11 = sug ++, 11 1 = sug +	15 exams sugar + to ft tr 8 times
7	A S	♀	21	11/20/13 11/22/13 7/13/15			081	100	071	79 = sug 0, 9-11 = sug 0, 11 1 = sug 0	2 wks after drop in temp pulse remains up 2 exams no sugar
8	M W	♂	40	12/18/13 12/22/13 2/25/14				109 106	111	79 = sug 0, 9 11 = sug +, 11 1 = sug +	45 exams ft tr sugar 15 times
9	A H	♀	19	1/24/14 1/27/14			083		088	79 = sug 0, 9 11 = sug 0, 11 1 = sug 0	5 exams no sugar
10	C H	♀	23	2/24/14 3/12/14				133	226	79 = sugar 1.8%, 9 11 = sugar 1.4%, 11 1 = sugar ft tr, 13 = sug 0	49 exams ft tr sugar 7 times
11	K L	♀	44	4/23/14 5/26/14				115	147	50 gm glucose, 50 gm bread, 50 gm cereal 8 10 = sug +, 10-12 = sug +, 12 2 = sug + Left hospital after four days' stay against advice	26 exams ft tr to quantitative amount 11 times 3 exams no sugar
12	E L	♀	32	6/6/14			107			--	4 exams ft tr sugar twice
13	E S	♀	31	5/22/14 5/24/14			109	103		79 = sug +, 9 11 and 11 1 = sug 0	8 exams sugar 0
14	M S	♀	23	9/19/14 9/22/14			123		not obtained		

47 exams sugar 5 times

60 exams P O = sugar ft tr 3 times

5 exams sugar once

125 exams sugar marked tr to ft 41 times this appeared more often before operation and after first operation then subsequently Patient had 3 operations for thyroid condition

At end of 3 hrs blood sugar not obtainable Left hospital Showed sugar twice in 10 examinations

1 exams ft tr sugar twice Refused second phlebotomy sugar 0 8 exams sugar 0 thought to have been glomerular nephritis 12 exams sugar 0 9% once

13 exams no sugar (urine always very scanty due to vomiting) 3 exams no sugar Discharge diagnosis = "dysserisia of organs of internal secretion" Many of the symptoms pointed toward exophthalmos, this seems the more probable diagnosis 22 exams no sugar

11/13/12 to 12/31/12 sugar found every day from 0.1% to 0.7% Carbohydrate intakes less than 60 gm

15	L S	Q	30	5/10/15 5/19/15	106 107	216	103	138 gm carbohydrate in diet 100 gm glucose + breakfast sug tr, 4 p m to 7 a m = sug tr 123 gm carbohydrate in diet 811 = sugar 1.2%, 111 = sug tr, 1.3 = sugar 0 (100 gm glucose, fasting) 227 gm carbohydrate in diet
16	L B	Q	40	5/31/15 10/ 8/14 10/ 8/14 4/12/15 4/14/15	117 118 104	106	110	79 = sugar 0.5%, 911 = sug ft tr, 113 = sug ft tr 100 gm glucose + breakfast 810 = sug t, 101 = sug 0 p e without glucose 810 = sug 0, 1012 = sug 0 75 gm glucose + breakfast 812 = sug t, 127 a m = sug 0 200 gm carbohydrate in diet past 4 days 100 gm carbohydrate in diet past 2 days
17	D W	Q	31	3/ 5/15	113			Further observation impossible, left hospital against advice
18	M B	Q	23	6/10/13 6/19/13 6/25/13 10/24/13 10/28/13 11/10/13 11/15/11	117 116 111 118	108	115 119	Had been on diet of 15 gm carbohydrate for 5 days prev 79 = sug ft tr, 911 and 111 = sug 0 170 gm glucose 79 = sug t, 91 = sug tr, 13 = sug 0 160 gm carbohydrate past 2 days 810 = sugar 0.4%, 102 = no sugar After 3 days of 10 gm carbohydrate in diet After 4 days of 102 gm carbohydrate in diet
19	E M	Q	43	5/19/15 6/23/15	101 125			911 = sugar 1.5%, 111 = sugar 1%, 13 = sugar 0.8%, 36, 68, 810 = sugar t 10 p m - 7 a m = sugar t, 7-10, 123, 36 = sugar t 6 p m - 7 a m = sugar tr, 71 = sugar ft tr, 11 = no sugar 810 = sugar 1.2%, 102 = sugar 0.5%
20	M O	Q	43	7/17/15 2/10/14 2/ 7/	113	224	135	810 = sug t, 1012 = sug t, 122 = sug 0
21	M F	Q	39	2/12/15 2/19/	095			810, 1012, 122 = sugar 0
22	E M	Q	40	1/14/14 1/20/			097	79 = sug ft tr, 911 = sug ft tr, 111 = sug 0
23	S S	Q	55	1/23/15 2/ 6/	094 115			Because of vomiting, glucose test could not be given
24	A P	Q	58	9/30/14 10/ 2/			116	79 = sug tr, 911 = sug marked tr, 111 = sug tr
25	G N	Q	25	2/11/15	076			--
26	O W	Q	39	12/ 4/12 12/21/			097 095	--
27	L R	Q	22	4/21/13			107	

spontaneous or alimentary glucosuria at some time during their stay in the hospital. This last statement does not apply to cases of diabetes, which, although they may be sugar-free in the urine, continue to show a hyperglycemia. Nor does it apply to certain cases of nephritis in which the hyperglycemia is probably due to an impermeability of the kidneys. Certain cases of myxedema studied in this connection also show quite marked hyperglycemia on thyroid treatment without the appearance of sugar in the urine. This last observation is one that is difficult to explain.

There are twenty of the severe or moderately severe cases. Eighteen show a hyperglycemia, either fasting or from two and a half to three hours after breakfast. They all show either an alimentary or spontaneous glucosuria in most of the cases both. And further all those on whom the test was made show an increase above the pre-existing blood-sugar level two hours after 100 gm of glucose, which was proportionally much greater than in any of the normal controls, most of whom showed a return to preformed values after this test. The alimentary glucosuria was usually quite marked, and in one patient persisted for three days.

In one case of the moderately severe type, Case 7, A. S., who did not show the foregoing changes, the patient was studied two or three weeks after the onset of symptoms and reacted precisely as did the normal controls. A year and a half later, although the symptoms were much milder, she showed 0.1 per cent of blood sugar three hours after a very light breakfast. No opportunity has been offered to study the urine consecutively in this case. The other patient A. H. (Case 9), had been operated on twice before she came under observation and, although improved as compared with her preoperative condition, still had active symptoms. She never showed any alteration in carbohydrate tolerance.

Of the mild cases, three show distinct lowering of the carbohydrate tolerance as shown by alimentary and spontaneous glucosuria, and in two cases there was an alimentary hyperglycemia.

Case 26, C. W. showed a daily glucosuria for almost six weeks on a carbohydrate intake which never exceeded 60 gm and very often was not more than 20 gm. This glucosuria was as high as 0.7 per cent and yet the blood sugar never was above 0.097 per cent two and a half hours after a light breakfast. It is unfortunate that this patient and A. C. (Case 24) in Table 1, who showed a faint trace of sugar, spontaneously and induced, were not studied at five or ten minute intervals after eating. It may be that their postprandial curves were very high and abrupt, as in some of Jacobsen's patients, and that during this time the kidney threshold for sugar was overstepped or

that in certain individuals the kidney is permeable to sugar when the glycemia is within the limits of normal

Cases 4, 5, 16 and 18 emphasize the point that, synchronous with decided clinical improvement, the tendency to hyperglycemia and glucosuria is reduced, lower blood-sugar values and a decreased tendency to glucosuria being noted in postoperative periods when temporarily at least, the patient is much better

The influence of diet, especially of carbohydrate food, is of some importance, as Jacobsen¹⁰ and Strouse¹¹ have pointed out for both normal and pathologic cases. In the earlier cases it was not possible to control this accurately, but roughly the carbohydrate intake ranged from 100 to 300 gm, averaging 150 gm daily. Lately accurate estimation of diets has been possible and in two cases, L B (Case 16) and M B (Case 18), their effect can be noted

Patient 6, R B, with very severe symptoms, who subsequently died after operation shows a blood-sugar reading of 0.086 per cent the day after admission to the hospital. She had been eating very little for some days, and this may explain the normal figures obtained. Always after this she showed marked intolerance to carbohydrates, and hyperglycemia

The hyperglycemia and glucosuria produced by psychic stimuli, such as fear, emotion, etc., as shown in animals by Schaffer¹² and Cannon,¹³ is to be considered in interpreting the foregoing results. That this factor would be more apt to influence cases of hyperthyroidism than normal individuals is self-evident. But even granting that venipuncture was responsible for the hyperglycemia found, it could hardly explain the alimentary or spontaneous glucosuria. Moreover, in all the cases studied, every precaution was taken to reassure patients, and evidences of undue excitement, such as increased pulse rate, nervousness, etc., were rarely seen. In one instance, R B, Case 6, Table 2, noted above, whose initial blood-sugar reading was 0.086 per cent, showed as much apprehension if not more at this time than any of the other patients. And in this case the blood sugar was normal. M B (Case 18) and L S (Case 15) objected to venipuncture, but it never seemed to excite them.

There are various hypotheses which can be advanced to explain the production of hyperglycemia in hyperthyroidism: (1) the secretion of the thyroid acting on the suprarenals stimulating them to

10 Jacobsen, A. T. B. *Biochem. Ztschr.*, 1913, lvi, 471.

11 Strouse, Solomon. *Bull. Johns Hopkins Hosp.*, 1915, xxvi, 211.

12 Schaffer, P. A. *Jour. Biol. Chem.*, 1914, xix, 296.

13 Cannon, W. B., Shohl, A. T., and Wright, W. S. *Am. Jour. Physiol.*, 1911, xxix, 280.

TABLE 3--BLOOD-SUGAR DETERMINATIONS IN FOUR CASES OF HYPOTHYROIDISM

Case	Name	Sex	Age	Date	Diagnosis	Blood Sugar Percentage					Urine at 2 hr Intervals Post 100 gm Glucose, Three Specimens	Daily 24 Hr Urine
						Fasting	1 Hr p c	2 Hrs p c	2½ Hrs p c	3 Hrs p c	2 Hrs Post 100 gm Glucose	
1	M K	♀		6/23/14 6/25/14	Myxedema --		.	..	110		79 = sug tr, 9-11 = sug v ft tr, 111 = no sugar	Had been on thyroid ext 6 wks before observed Symptoms of acute hyperthy- roidism at time, No sugar (4 mos)
2	A F	♀		1/26/15 1/28/15	Obesity Myxedema ?	053					150 gm glucose 79, 911, 111 = no sugar	Thyroid begun 2/4/15, stopped 4/9/15, Patient lost 21 lbs Thyroid started 5/5/15, stopped 5/24/15
				2/ 1/15							200 gm glucose = no sugar, 810, 1012, 122 = no sugar	
				2/ 3/15							250 gm glucose 810 = sug tr, 10-12 = sug ft tr, 122 = no sugar	
				2/14/15	--	112					810, 1012, 122 = no sugar	
				2/19/15				159			810, 1012, 122 = no sugar	
				3/13/15	--						810, 1012, 122 = no sugar	
				3/15/15							79, 911, 111 = no sugar	
				3/19/15								
				3/27/15								
				4/ 2/15	--							
				4/14/15		106		116				
3	M R	♀	47	2/15/15 3/26/15	Myxedema	090 120					Before thyroid treatment After thyroid treatment (8 days)	No sugar (5 days) No sugar (1 day)
4	J H	♂	38	10/ 3/14 10/ 7/14	Myxedema ? --						810, 1012, 122 = no sugar 810 = no sug, 10-12 = marked tr sug, 122 = no sugar	No sugar, 2 exams

† After 200 gm glucose

increased activity, (2) an inhibitory action on the sugar-metabolizing powers of the pancreas, (3) it may produce its effect by action on some other of the endocrine glands concerned in sugar metabolism

Allen⁴ concludes that lowered tolerance to carbohydrates in exophthalmic goiter can be explained on a toxic or nervous basis, being more inclined to favor direct action of the thyroid secretion on the nervous system Falta¹⁴ favors the theory of direct action of the thyroid secretion on the pancreas

It is not the purpose of the present article to discuss the various views pro and con on this subject, but whatever the mechanism of the production of hyperglycemia and general tendency to lowered tolerance for carbohydrates may be, there is one fact that stands out clearly from a study of Table 3, which is that thyroid extract produces in cases of hypothyroidism a very definite hyperglycemia, when, as shown in two cases, a low to normal blood sugar had previously existed (fasting) In Case 4, J H, there was a low blood sugar two hours after 100 gm of glucose, and a hyperglycemia two hours after 200 gm of glucose This patient did not receive thyroid extract It is interesting to note that in the cases receiving thyroid extract the production of hyperglycemia was not accompanied by any toxic symptoms

CONCLUSIONS

1 The normal blood-sugar values reported to date are as a rule much higher than those found in this paper The extremes reported range from 0.04 per cent to 0.13 per cent Great diversity of methods and other factors mentioned above probably account for this The general adoption of a uniform method for blood-sugar determinations is an urgent clinical need A blood-sugar reading of 0.1 per cent or over is to be considered a hyperglycemia

2 Hyperglycemia is a very common accompaniment of hyperthyroidism In the moderate and severe types of this disease, it occurs in 90 per cent of the cases studied. In mild cases or during latent periods, normal blood-sugar values are commonly obtained

3 Glucosuria, either spontaneous or alimentary (100 gm of glucose), is an equally constant symptom, and encountered much more often than has been observed hitherto

4 Alimentary hyperglycemia (two hours after 100 gm of glucose) and alimentary glucosuria are found not uncommonly in the very mild cases, whereas hyperglycemia (fasting or postprandial) and spontaneous glucosuria are usually absent

14 Falta Quoted by Allen (Footnote 4)

5 As compared with normal individuals, there is a slower return to fasting blood-sugar values after doses of glucose have been given. This is more marked in proportion to the severity of the case.

6 Thyroid extract when fed to patients with myxedema, who previously showed normal blood-sugar values, produces hyperglycemia similar to that found in cases of hyperthyroidism.

7 The diagnostic significance of lowered tolerance to carbohydrates in hyperthyroidism is of great importance. The finding of glucosuria and hyperglycemia in other pathologic conditions, such as fever, alcoholism, asphyxia, neurasthenia and in the various endocrinopathies, somewhat nullifies its significance, but if these conditions can be excluded, its presence is highly suggestive.

THE PRODUCTION OF ATRIOVENTRICULAR RHYTHM IN MAN AFTER THE ADMINISTRATION OF ATROPIN¹

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INTRODUCTION

Atrioventricular rhythm has been investigated in the experimental animal by a large number of observers. Among these are Lewis,¹ Zahn,² Williams and James,³ Ganter and Zahn,⁴ Meakins,⁵ Rothberger and Winterberg,⁶ Eyster and Meek,⁷ and others. It has usually been produced experimentally by slowing the rate at which the impulses are sent out from the sino-auricular node or by preventing the spread of such impulses to other parts of the heart. The following methods have been employed for this purpose: (1) cooling the sinus node with an ice pencil or by means of the ethyl chlorid spray, (2) crushing or excising the sinus node, or (3) isolating the sinus node by making cuts about it. Atrioventricular rhythm has also been produced by stimulation of the right vagus^{1, 7} and by stimulation of the left accelerator.⁶ We shall not discuss these observations in detail but wish to point out a few facts which they have established.

The reason why any of the above procedures may produce an A-V rhythm is plain when we understand that the A-V node, like the sinus node, has the property of elaborating impulses at regular intervals. Ordinarily this property of the A-V node is entirely latent because of the greater rhythmicity of the sinus node. The frequent stimuli which descend from the latter constantly destroy the stimulus material which accumulates at the A-V node before it has reached the level necessary

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1 Lewis, T. The Effect of Vagal Stimulation upon Atrio-Ventricular Rhythm, *Heart*, 1914, v, 281.

2 Zahn. Experimentelle Untersuchungen am Säugetierherzen über Reizbildung und Reizleitung im Atrio-ventricularknoten, *Arch. f. d. ges. Physiol.*, 1913, cli, 247.

3 Williams and James. Reversal of the Cardiac Mechanism, *Heart*, 1914, v, 109.

4 Ganter and Zahn. Experimentelle Untersuchungen am Säugetierherzen über Reizbildung und Reizleitung in ihrer Beziehung zum spezifischen Muskelgewebe, *Arch. f. d. ges. Physiol.*, 1912, cxlv, 335.

5 Meakins. Experimental Heart-Block with Atrioventricular Rhythm, *Heart*, 1914, v, 281.

6 Rothberger and Winterberg. Ueber die Beziehung der Herznerven zur Atrio-ventriculären Automatie, *Arch. f. d. ges. Physiol.*, 1910, cxxxv, 559.

7 Eyster and Meek. Experiments on the Origin and Propagation of the Impulse in the Heart, *Heart*, 1914, v, 227.

for the formation of an impulse. The rate of the latent inherent rhythm of the A-V node has been called its "period" (Williams and James³). It may be very close to the rate of the sinus rhythm or it may be considerably below it. To produce A-V rhythm it is necessary either to reduce the rate of the sinus rhythm below the period of the A-V node or to increase the period of the A-V node above the rate of the sinus rhythm. The center which forms impulses most rapidly acts as pace-maker for the remainder of the heart. In most of the experimental studies previously referred to, A-V rhythm was produced by the first method. When A-V rhythm is produced by accelerator stimulation, however, the second method is the one employed.

Animal experimentation has also shown that most of the delay between auricular and ventricular systoles during the normal rhythm takes place within the A-V node (Hering⁸). Corresponding to these observations it has been found that in A-V rhythm the P-R interval of the electrocardiogram is reduced and the amount of reduction depends on the level in the node at which the abnormal rhythm originates. Depending on the site of origin, therefore, three types of A-V rhythm may be distinguished: in the first, which originates in the upper portion of the node, the P-R interval is present but reduced, in the second, which originates in a lower portion of the node, the P-R interval is zero, and in the third, which originates in the lowest portion of the node or in the main stem of the His bundle, the P-R interval is negative. It has also been shown by Meakins⁵ that the auricular complex of the electrocardiogram in A-V rhythm is usually inverted. Two criteria, then, for the recognition of clinical A-V rhythm have been established experimentally: reduction or reverse of the P-R interval and inversion of P.

Clinically, atrioventricular rhythm is comparatively rare. There are two distinct varieties. The first of these is the heterogenetic type, or paroxysmal tachycardia of A-V origin, which is characterized by its rapid rate and the abrupt change in heart rate at the onset and end of an attack. During the abnormal rhythm the rate of the heart is not under the control of the extrinsic cardiac nerves. Paroxysmal tachycardia originating in the A-V node has been observed in man by Lewis,⁹ by Cohn,¹⁰ and by Rühl.¹¹

8 Hering. Nachweis dass die Vergögerung der Erregungsüberleitung zwischen Vorhof und Kammern des Säugetierherzens in Tawara'schen Knoten erfolgt, *Arch f d ges Physiol*, 1910, cxxx, 572.

9 Lewis. Auricular Fibrillation and Its Relationship to Clinical Irregularity of the Heart, *Heart*, 1909-1910, 1, 306, Paroxysmal Tachycardia, Accompanied by the Ventricular Form of Venous Pulse, *Heart*, 1910-1911, 11, 127.

10 Cohn. A Case of Paroxysmal Tachycardia, *Heart*, 1910-1911, 11, 170.

11 Rühl. Ueber atrioventriculäre Tachycardie beim Menschen, *Deutsch med Wchnschr*, 1907, xxxv, 632.

The second variety of A-V rhythm is the homogenetic type which is characterized by its comparatively slow rate and by the very gradual change in heart rate at its onset and end. Moreover, the rate of the heart is under the control of the extrinsic cardiac nerves during the abnormal rhythm. A-V rhythm of this type has been observed in man by Lewis,¹² Belski,¹³ Hume,¹⁴ Williams and James,³ Laslett,¹⁵ Weil,¹⁶ and others. It seems to be most common in acute infectious diseases, especially diphtheria. It has been produced in man by forced respiration¹⁷ and by ocular pressure.¹⁸ It has also been noted after the administration of atropin^{18, 19}. A-V rhythm of this type is comparable in every respect to that produced in animals by the methods previously mentioned.

In the present article we wish to describe a method by means of which A-V rhythm of the homogenetic type may be produced in a large proportion of young adults. In brief this method consists in stimulation of the vagus at a certain period of atropin action which begins about eight minutes after, and ends about twenty minutes after the hypodermic administration of 1 mg of atropin sulphate. Our results indicate that at this period of atropin action the period of the A-V node closely approaches the rate of the sinus rhythm.

MATERIAL AND METHODS

The material for this report was obtained by the administration of atropin to eighteen men and two women between the ages of 20 and 28. Of these patients 1 to 13 inclusive were in good health and had no symptoms or signs referable to cardiac disease. Patients 14 to 17 inclusive complained of rapid heart action at times but had no other cardiac symptoms or signs. Patient 18 was under treatment for latent syphilis; there were no signs of heart involvement. Patients

12 Lewis. Clinical Electrocardiography, London, 1913, p. 73.

13 Belski. Beobachtungen über atrio-ventriculäre Automatie im Verlauf der Infektionskrankheiten, Ztschr. f. klin. Med., 1909, lxvii, 515.

14 Hume. A Polygraphic Study of Four Cases of Diphtheria with a Pathological Examination of Three Cases, Heart, 1913-1914, v, 25.

15 Laslett. A Case Exhibiting a Slow Atrio-Ventricular Rhythm, Heart, 1915, vi, 81.

16 Weil. Beiträge zur klinischen Elektrokardiographie, Deutsch. Arch. f. klin. Med., 1914, cxvi, 486.

17 Wilson. Three Cases Showing Changes in the Location of the Cardiac Pace-Maker Associated with Respiration, THE ARCHIVES INT. MED., 1915, xvi, 86.

18 Gallavardin, Dufourt, and Petzetakis. Automatismes ventriculaires intermittents, spontanés ou provoqués par la compression oculaire et l'injection d'atropine dans le bradycardies totales, Arch. d. mal. du cœur, 1914, vii, 1.

19 Neuhof. A Case of Independent Ventricular Activity Occurring During Acute Articular Rheumatism, THE ARCHIVES INT. MED., 1915, xv, 169.

19 and 20 had definite physical and electrocardiographical signs of heart disease and will be discussed separately

Each patient, while under observation with the electrocardiograph, was given approximately 1 mg of atropin sulphate by hypodermic injection and the movements of the galvanometer string were closely watched, and any change in heart mechanism observed was recorded photographically. If no change was noted records were taken at intervals of one or two minutes for from twenty to thirty minutes. At short intervals during the experiment the patient was asked to take a very deep breath and hold it, or pressure was made on the right eyeball. These procedures were carried out in an attempt to determine whether vagus stimulation during the early period of atropin action would produce in the normal heart an A-V rhythm, such as appeared spontaneously under this drug in two pathologic cases described later. The effect of vagus stimulation on the heart mechanism before the atropin was given was also determined.

PRODUCTION OF A-V RHYTHM IN YOUNG ADULTS WITH APPARENTLY NORMAL HEARTS

It was found that at a certain period of atropin action A-V rhythm could be produced in a large proportion of the cases investigated. In nine subjects it was produced by forced respiration, in two by right ocular pressure, and in one it appeared spontaneously. Ocular pressure, because of the discomfort that it produced, was employed in only a few cases. Five of our experiments were negative. In none of these cases could an A-V rhythm be produced by vagus stimulation before atropin had been given, although single idioventricular beats or considerable flattening out of the P wave sometimes occurred. The period of atropin action during which an A-V rhythm could be produced varied greatly, but usually the abnormal rhythm was most easily obtained between eight and fifteen minutes after the drug had been given. The exact period over which it could be produced was not determined because it was often impossible to recognize the abnormal rhythm by observing the movements of the galvanometer string, and continuous records were not taken. In a large proportion of the subjects forced respiration was repeated at intervals during the experiment until the abnormal rhythm could no longer be produced, which was usually about twenty minutes after the drug had been given. A-V rhythm could not be produced beyond this point and during the maximum effect of the atropin. The subjects were not selected except that young people were chosen.

TYPES OF A-V RHYTHM

The A-V rhythms obtained by this method may be divided into three classes (a) A-V rhythm in which the P-R interval was present but reduced, (b) A-V rhythm in which the P-R interval was zero and (c) A-V rhythm in which there was an R-P interval

The first type of A-V rhythm was observed in nine subjects. It is illustrated in Figure 1. Figure 2 illustrates the normal mechanism before atropin and Figure 3 the normal mechanism after the atropin

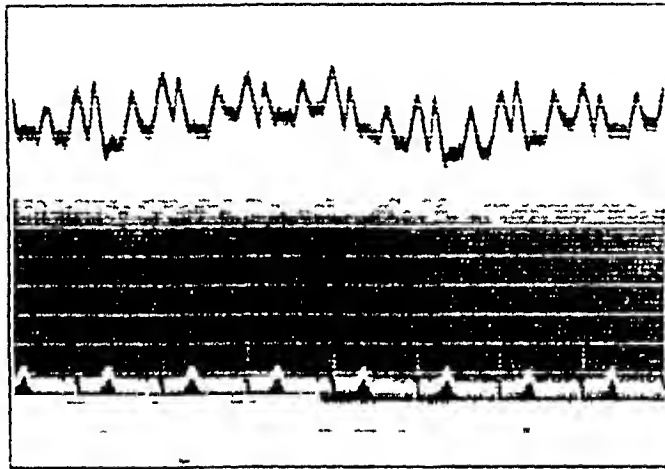


Fig 1—Subject 14, Lead 3. A-V rhythm of Type 1 which occurred spontaneously after atropin. P-R equals 0.13 second, a-c equals 0.15 second. Heart rate 94.

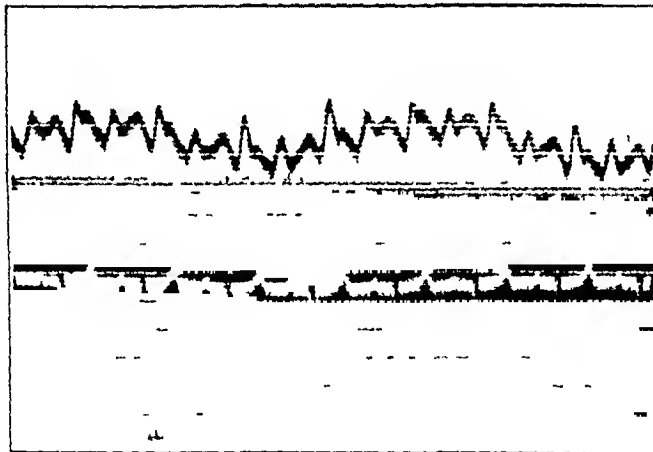


Fig 2—Subject 14, Lead 3. Taken before atropin was given. The P-R interval is 0.19 second. The a-c interval is 0.20 second. The heart rate is 94.

effect had reached its maximum. This A-V rhythm appeared spontaneously after atropin (Patient 14). The P-R and a-c intervals are reduced and P is inverted.

A-V rhythm of the second type is illustrated by Figure 4 from Patient 8. In this figure P is not seen during the abnormal mechanism because it occurs simultaneously with R as is shown by the tall composite a wave in the jugular pulse. The abnormal rhythm in this case

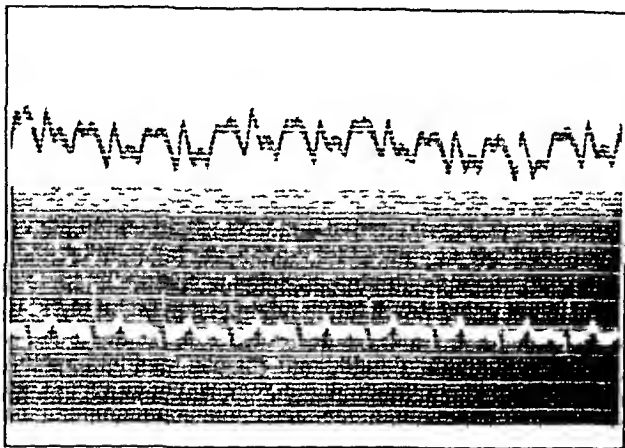


Fig 3—Subject 14, Lead 3 Normal rhythm at the time of the maximum atropin effect Heart rate 112

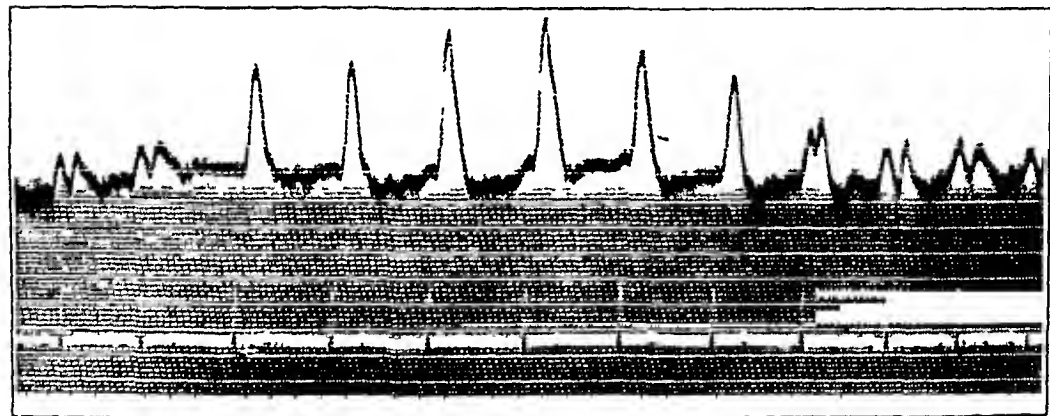


Fig 4—Subject 8, A-V rhythm of Type 2 produced after atropin by right ocular pressure During the abnormal rhythm P is not seen but a large wave in the venous pulse shows that auricles and ventricles contracted simultaneously Heart rate during the abnormal rhythm 78

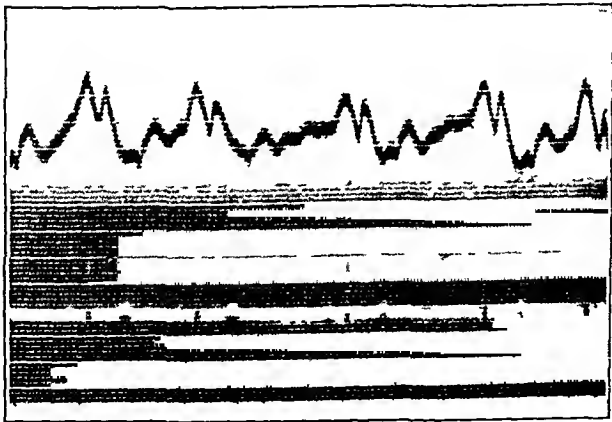


Fig 5—Subject 8, Lead 3 Taken before atropin was given P-R equals 0.15 second, a-c equals 0.15 second Heart rate 58

was produced by right ocular pressure. Short periods of A-V rhythm alternated with short periods of normal rhythm for several minutes after the ocular pressure was made. In Figure 5 the normal rhythm before atropin is shown and in Figure 6 the heart mechanism at the time of the full atropin effect is seen. Figure 7 shows the effect of right ocular pressure before atropin. The third cycle is an idioventricular beat as there are no P nor *a* waves accompanying it. The a-c intervals of the sixth and eighth cycles are reduced showing that the ventricle escaped in each instance. It will be noted that there may be

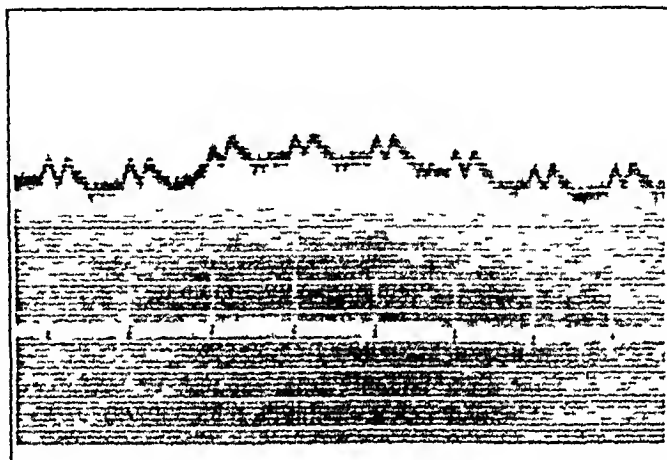


Fig 6—Subject 8, Lead 3. The normal rhythm at the time of the maximum atropin effect. Heart rate 100.

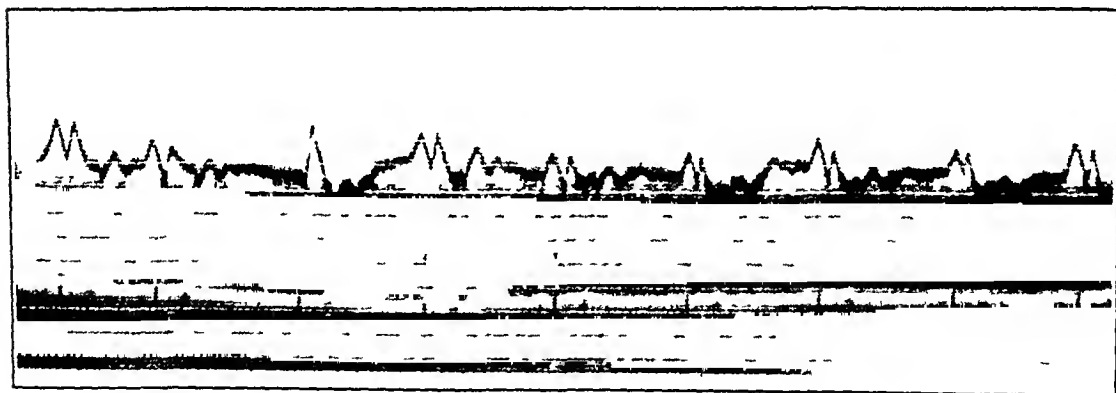


Fig 7—Subject 8, Lead 3. The effect of right ocular pressure before atropin. No A-V rhythm was produced but single idioventricular beats occurred (Cycles 3, 6 and 8). In Cycle 7 there is a marked flattening out of P without any corresponding change in the *a* wave.

very marked flattening out of the P wave of the electrocardiogram without any corresponding change in the venous pulse during vagal stimulation (Cycle 7), which confirms a view expressed by me in a previous article that this change in the shape and size of the P summit during vagal stimulation was not due to a diminution of the contractility of the auricles but to a change in the location of the pacemaker or an abnormal spread of the contraction wave over these chambers. An A-V rhythm of Type 2 was observed in five subjects.

The third type of A-V rhythm was observed in two subjects. It is illustrated by Figures 8, 9 and 10, all from Patient 7. P is inverted and follows R during the abnormal mechanism in Leads 2 (Fig 9) and 3 (Fig 10), and is invisible in Lead 1 (Fig 8). In the venous pulse there is a tall wave which has a broader summit than those seen in Figure 4. In Figures 8 and 9 transitions from the abnormal to the normal mechanism are seen and the end of a transition from the normal to the abnormal mechanism is seen in Figure 9. It will be

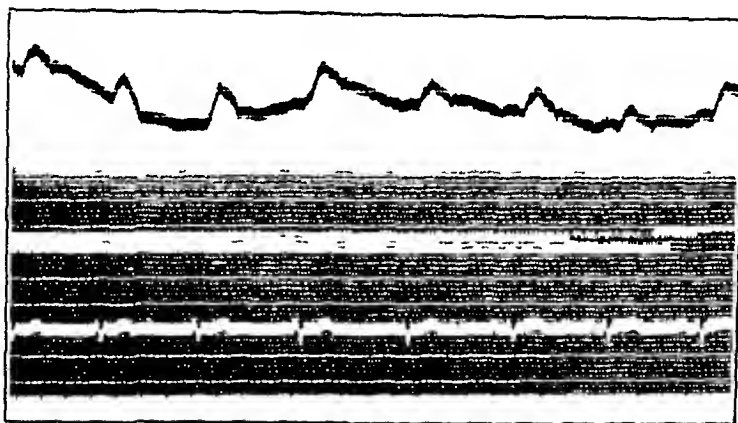


Fig 8—Subject 7, Lead 1. A-V rhythm produced by deep respiration during an atropin experiment. P is invisible during the abnormal rhythm.

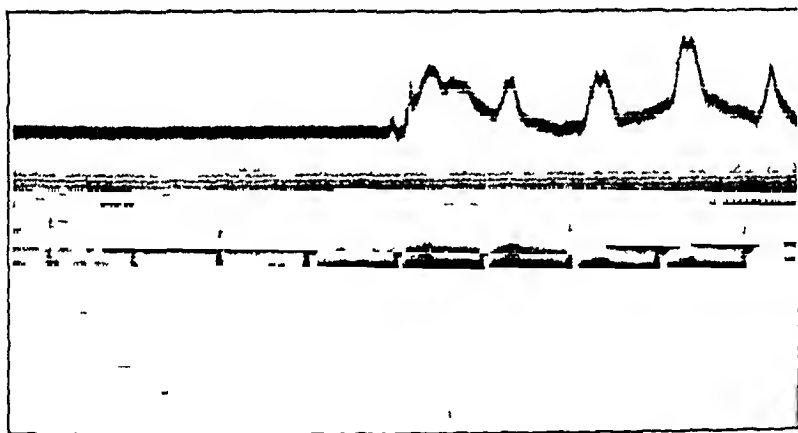


Fig 9—Subject 7, Lead 2. A-V rhythm of Type 3 produced after atropin by deep respiration. During the abnormal rhythm P is inverted and appears after R. The R-P interval is 0.05 second. The heart rate during the abnormal rhythm is 75. At the beginning of the figure the end of a transition from the normal to the abnormal rhythm is seen. P appears after R as a summit in the first two cycles.

noted that in the first two cycles of this figure, P appears after R as a summit. This indicates that the auricular contractions which produced these Ps were responses to the sinus node rather than to the A-V node, as were those which followed, which are represented by inverted Ps. The normal mechanism in this case is shown in Figure 11, which was

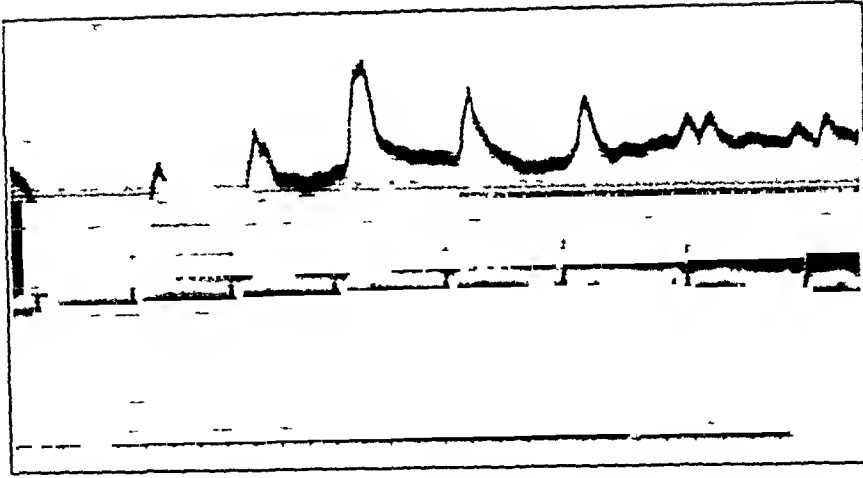


Fig 10—Subject 7, Lead 3 A-V rhythm of Type 3 produced by forced respiration after atropin P appears after R and is inverted during the abnormal rhythm In the venous pulse there is a single tall wave with a broad summit A transition from the abnormal to the normal rhythm occurs

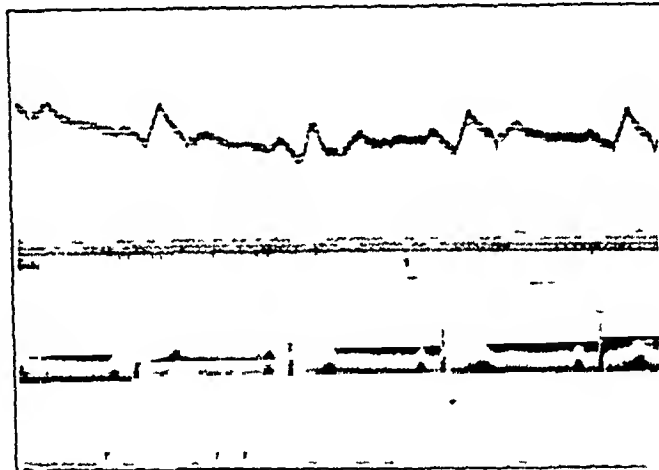


Fig 11—Subject 7, Lead 3 The normal rhythm before atropin The P-R interval is 0.17 second Heart rate 54

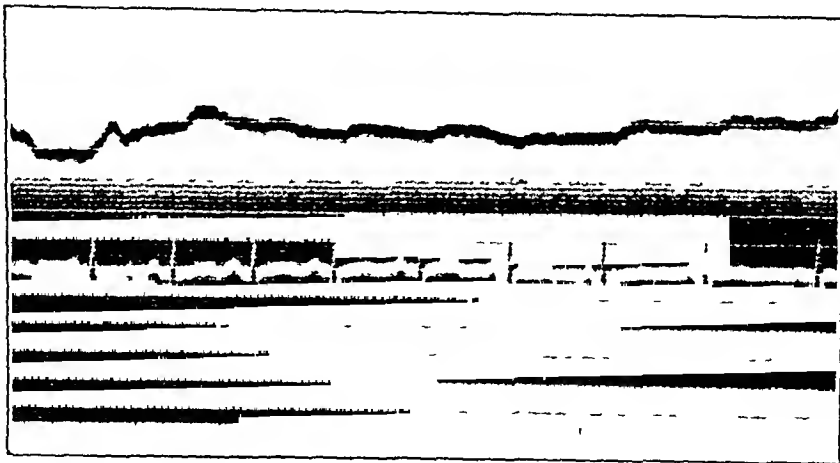


Fig 12—Subject 7, Lead 3 The effect of a deep breath 18 minutes after atropin A-V rhythm is no longer produced by this procedure There is still some vagus arrhythmia showing that the vagi are not completely paralyzed

taken before atropin was given and in Figure 12 the effect of a deep breath eighteen minutes after atropin is shown. At this time the A-V rhythm could no longer be produced although the vagi were not completely paralyzed as is shown by the presence of some respiratory arrhythmia.

The accompanying table contains a summary of the experiments on persons with apparently normal hearts. In some subjects more than one type of A-V rhythm was observed, in Subject 9 Types 1 and 2 both occurred and in Subject 13 all three types were recorded.

SUMMARY OF EXPERIMENTS ON PERSONS WITH APPARENTLY NORMAL HEARTS

Subject	A-V Rhythm			S-A Rhythm		A-V Rhythm Rate	S-A Rhythm	
	Type	P-R sec	a-c sec	P-R sec	a-c sec		Rate Before Atropin	Rate at End of Exper
1	1	0 13	0 15	0 15		54	85	92 †
2	1	0 13		0 16		66	63	70
3	1	0 16	0 19	0 19	0 21	60	52	60 †
4	1	0 12		0 14		80	75	†
5	0*							
6	2	0 00		0 17		66	75	109
7	3	0 05		0 17		75	54	100
8	2	0 00	0 00	0 15	0 15	78	58	100
9	1	0 11	0 13	0 15	0 17	63	60	73
	2	0 00	0 00	0 05	0 17	66		
10	2	0 00	0 00	0 16	0 19	92	75	92
11	1	0 15		0 17		80	85	100
12	0*							
13	1	0 10		0 13		75	75	85 †
	2	0 00		0 13		100		
	3	0 05		0 13		109		
14	1	0 13	0 15	0 19	0 20	94	94	112
15	1	0 13	0 13	0 15	0 15	100	100	109
16	0*							
17	0*							
18	0*							

* No A-V rhythm was produced

† A-V rhythm could still be produced when the experiment was terminated

The rate of the abnormal rhythm was usually intermediate between the normal rate before atropin and the sinus rate after the atropin effect had reached its maximum. The rates given in the table are only approximate, as the constant forced respiration during most of the experiments caused very marked fluctuations in heart rate even when the abnormal rhythm was present. These fluctuations made it impossible to compare the rate of the sinus rhythm and the rate of the A-V rhythm during the period when the latter could be produced. The A-V rhythm sometimes persisted for a very short period and was quickly replaced by the normal rhythm at a more rapid rate. Even when the abnormal rhythm appeared spontaneously it usually alternated with periods of normal rhythm and the heart rate varied constantly.

THE SPONTANEOUS APPEARANCE OF A-V RHYTHM AFTER ATROPIN IN TWO PATHOLOGIC CASES

In Patients 19 and 20 an A-V rhythm developed spontaneously after the administration of atropin. The complete histories and examinations of these patients have been given elsewhere¹⁷ and need not be repeated here. Patient 19 was a young man aged 22 who complained of occasional periods of rapid heart action. The examination of the

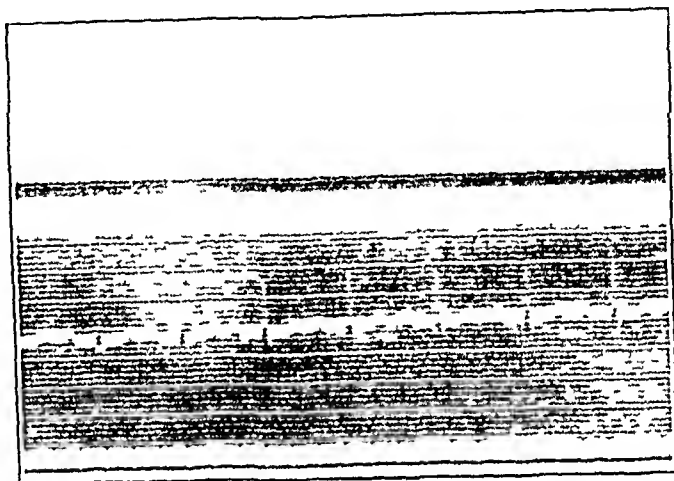


Fig 13—Subject 19, May 15, 1915, Lead 3. The normal rhythm before atropin. P-R equals 0.26 second.

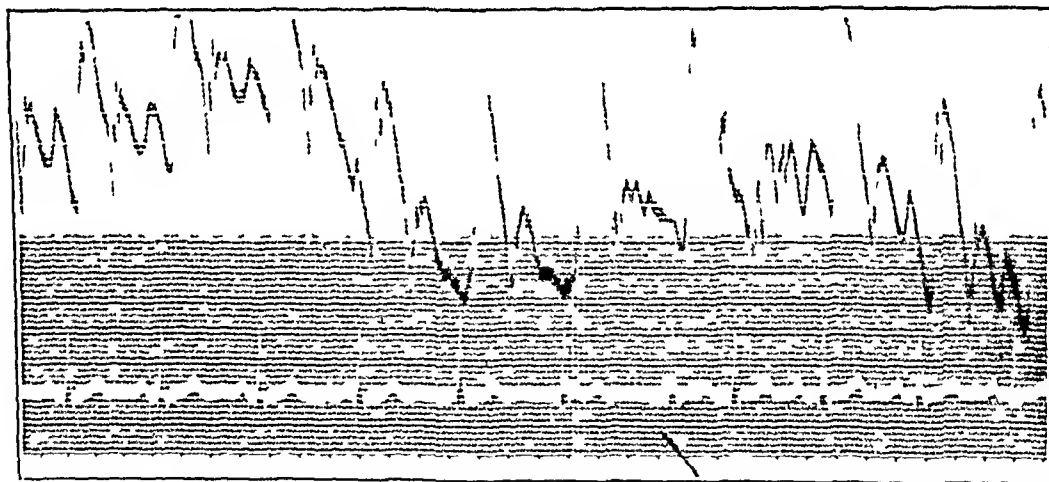


Fig 14—Subject 19, May 15, 1915, Lead 2. A period of auriculoventricular dissociation which occurred spontaneously after atropin. This dissociation begins with the fourth cycle and continues until P falls between R and T (Cycle 7). The eighth ventricular complex occurs as a response to the P which falls between R and T of the seventh cycle. During the period of dissociation the ventricles contract more rapidly than the auricles.

heart was negative except for the electrocardiographic tracings which showed a marked prolongation of the P-R interval when the patient first came under observation. At this time deep respiration produced on some occasions auriculoventricular dissociation which was not entirely due to the heart-block present but to an increase in the rate of

the idioventricular rhythm. During these periods of dissociation the ventricles beat more rapidly than the auricles. The P-R interval at the time of the first examination (Fig 13) was 0.33 second.

One month after this observation was made the patient was again examined and the P-R interval was found to be only 0.26 second in duration. At this time no auriculoventricular dissociation could be

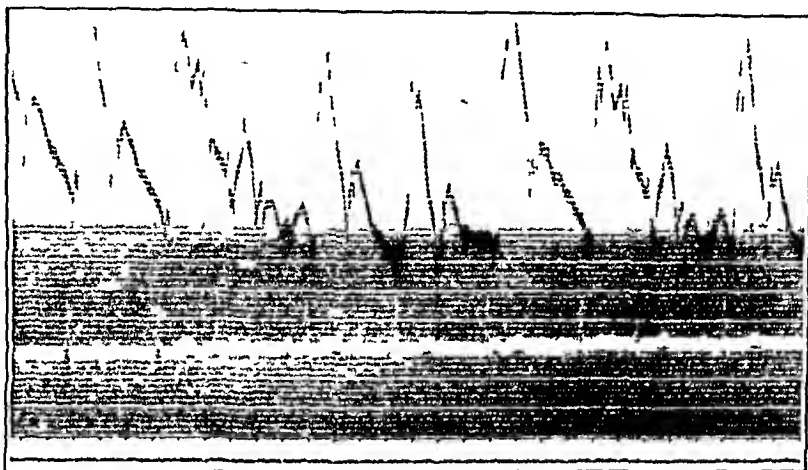


Fig 15—Subject 19, May 15, 1915, Lead 3. A period of auriculoventricular dissociation like that in Figure 14. The first ventricular complex which follows a period of dissociation is aberrant (ventricular complexes 3 and 8) and the P-R interval of these cycles is increased.

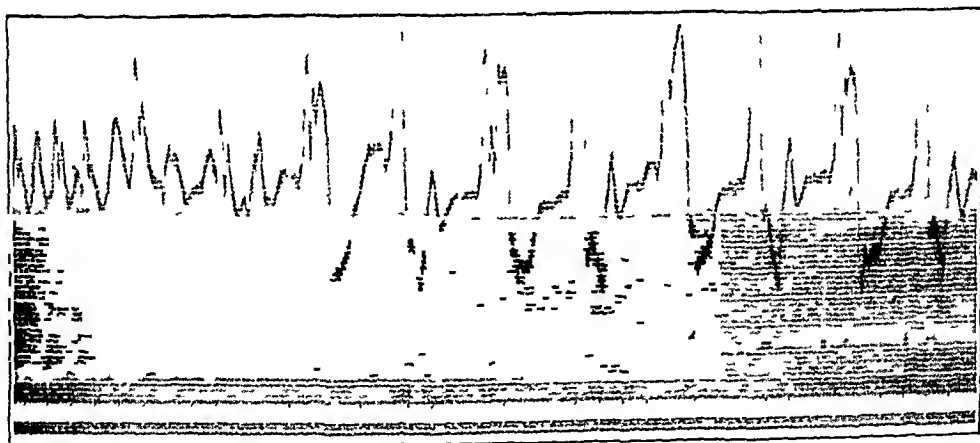


Fig 16—Subject 19, May 8, 1915, Lead 2. A period of auriculoventricular dissociation similar to those seen in Figures 14 and 15, except that the heart mechanism is complicated here by interference between the stimuli arising in the sinus node and those arising in the junctional tissues. The P waves which fall between R and T are deformed and sometimes diphasic (Cycle 6).

produced by deep respiration. The patient was given atropin (1 mg) hypodermically and periods of dissociation similar to those previously described appeared spontaneously about eight or nine minutes after the drug was given. This mechanism is illustrated in Figure 14. It will be seen in this figure that, because of escape of the idioventricular

hythm, P gradually approaches R and finally falls between R and T (Cycles 6 and 7) When P has reached this position the ventricles respond to the auricles (Cycle 8) and both chambers beat in unison for several beats after which the same process is repeated

The first ventricular contraction which followed such a period of dissociation (Cycle 8, Figure 14) was often characterized by an aberrant ventricular electric complex (Cycles 3 and 8 of Fig 15) and

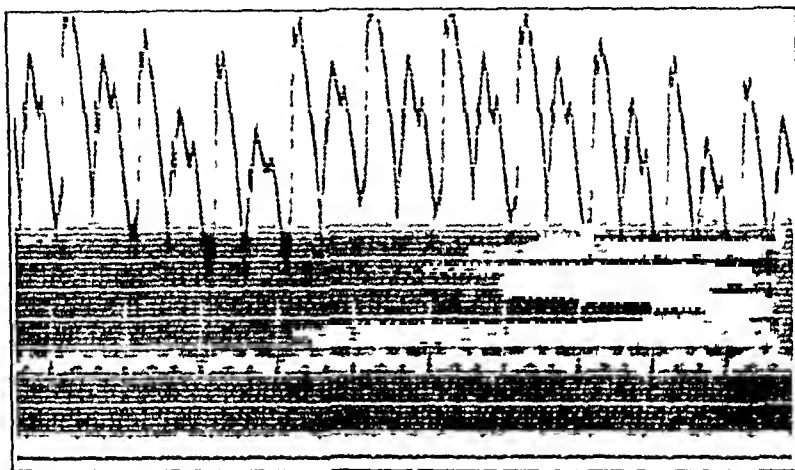


Fig 17—Subject 19, May 15, 1915, Lead 2 The heart mechanism at the time of the maximum atropin effect The P-R interval is still 0.25 second, showing that the block present in this case is organic

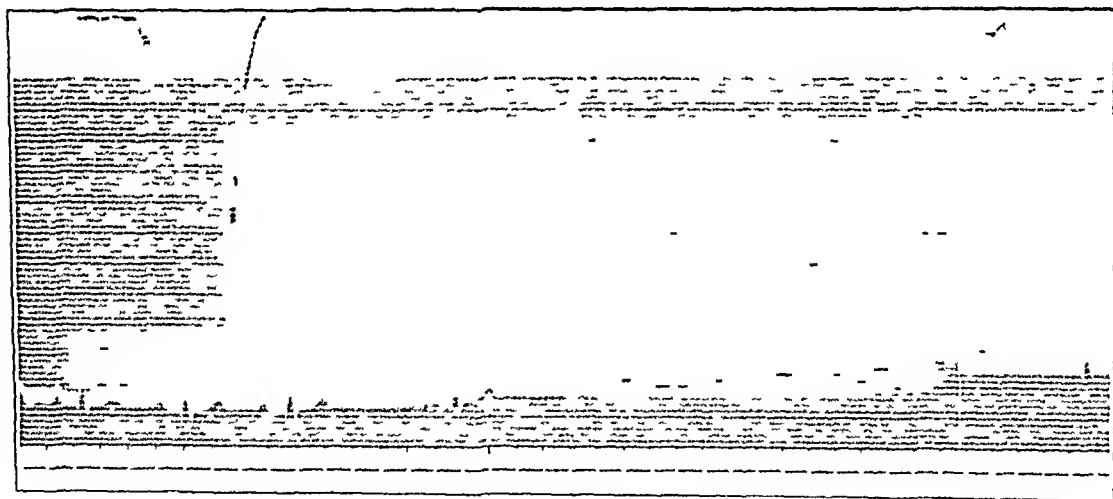


Fig 18—Subject 19, May 29, 1915, Lead 2 The effect of right ocular pressure The duration of the pressure is indicated at the top of the curve There is marked flattening out of the P waves during vagus inhibition The P-R interval of the normal rhythm (first two cycles) is now 0.21 second No A-V rhythm was produced by ocular pressure

the As-Vs time of these cycles was always increased (Figs 14 and 15) The failure of the stimuli arising at the sinus node and those arising in the junctional tissues to produce interference phenomena, which is the cause of this peculiar heart mechanism, may be explained by assuming that it was more difficult for stimuli to pass from the ven-

tricular side of the junctional tissues to the auricles than in the opposite direction. On some occasions such interference did occur, probably as a result of some change in the degree of block. When this happened the P's which fell between R and T were deformed and sometimes diphasic (Fig 16). The maximum atropin effect at the time of the second examination is shown in Figure 17. The P-R

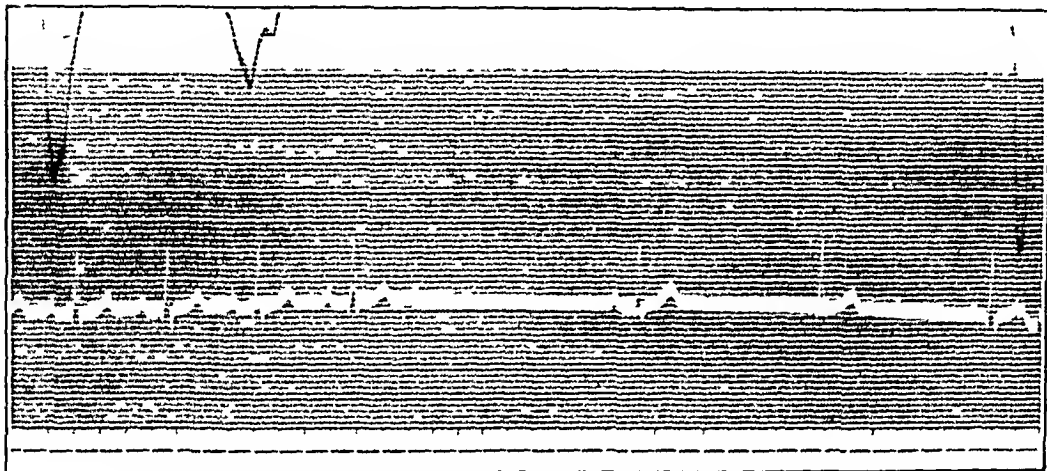


Fig 19—Subject 19, May 29, 1915, Lead 2. The effect of left ocular pressure. No A-V rhythm is produced. A single idioventricular beat is seen (Cycle 6).

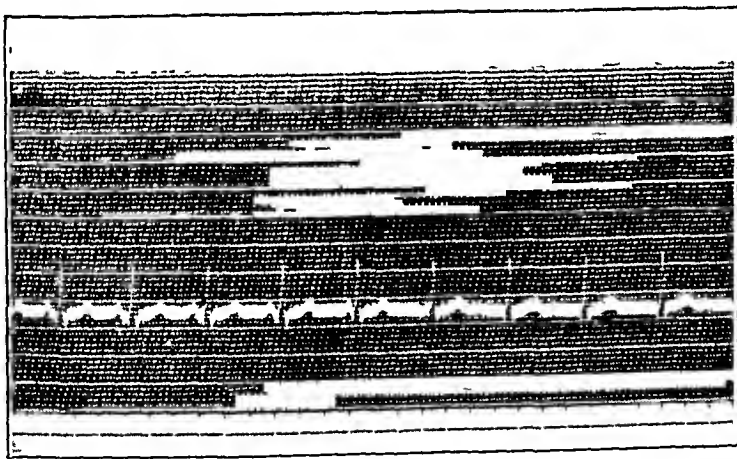


Fig 20—Subject 19, May 29, 1915, Lead 2. A-V rhythm of Type 2 which appeared spontaneously after atropin.

intervals in this figure are still 0.25 second indicating that the block present in this case was organic.

The patient was examined a third time one week after the second examination. The P-R interval at this time was 0.21 second. On this occasion an attempt was made to produce the abnormal mechanism by ocular pressure. The results of these experiments are shown in Figures 18 and 19. Single idioventricular beats are seen but no

definite A-V rhythm was produced. There was a marked flattening out of the P summits as a result of right vagus pressure (Fig 18) due either to dislocation of the pace-maker or to interference phenomena. Atropin (1 mg) was given hypodermically and about eight or nine minutes later an A-V rhythm of the type described as Type 1 appeared spontaneously (Fig 20). This rhythm could be slowed slightly by ocular pressure (Fig 21) showing that the A-V node was

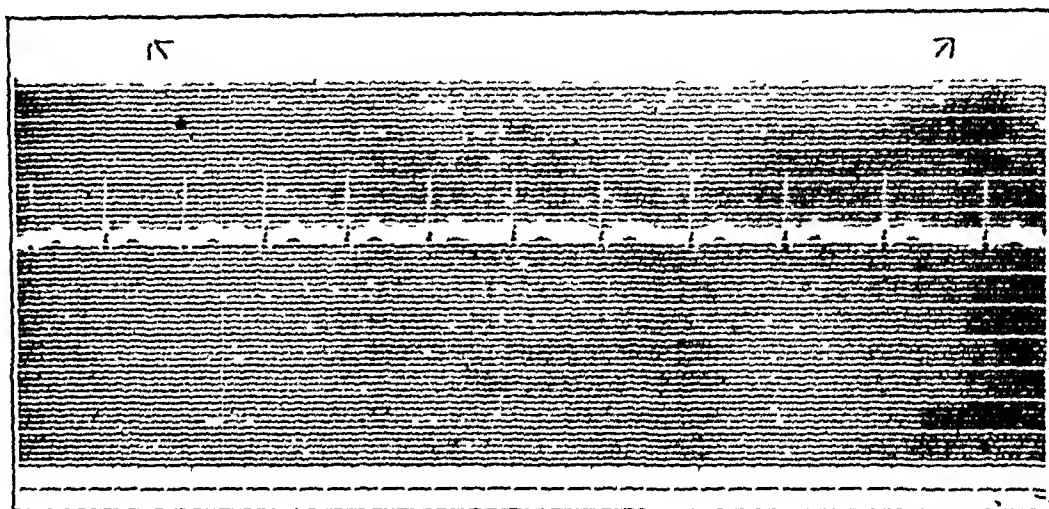


Fig 21—Subject 19, May 29, 1915, Lead 2. A-V rhythm of Type 2 which appeared spontaneously after atropin is slowed by left ocular pressure showing that the A-V node is still partially under vagus control.

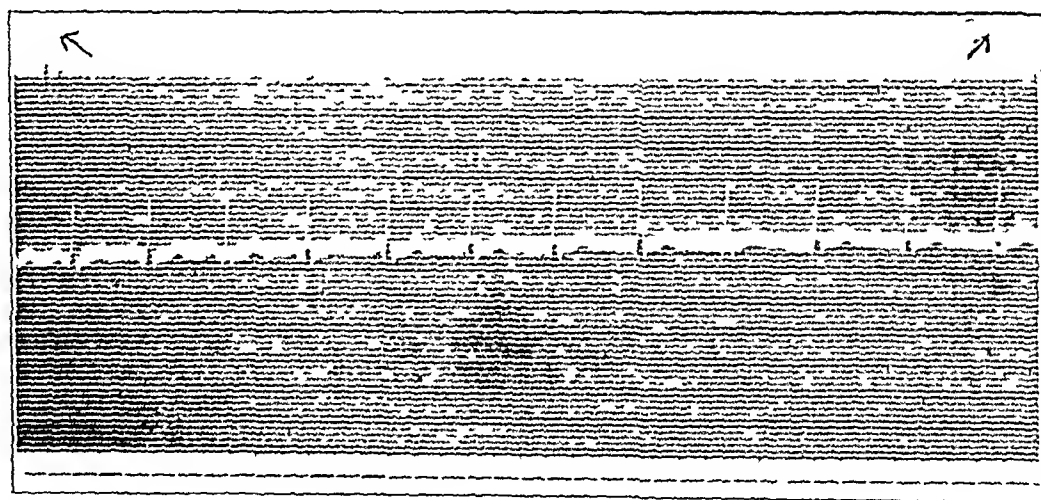


Fig 22—Subject 19, May 29, 1915, Lead 2. After the A-V rhythm had given place to the normal rhythm it could still be produced by right ocular pressure. The duration of the pressure is indicated by arrows.

still partially under vagus control. When the A-V rhythm gave place to the normal rhythm it could again be produced by ocular pressure either upon the right or left eye (Figs 22 and 23). The complete atropin effect was not obtained at the time of the third examination but although the abnormal rhythm appeared spontaneously at first



Fig 23—Subject 19, May 29, 1915, Lead 2 Same as previous figure except that the left ocular pressure was used instead of right ocular pressure

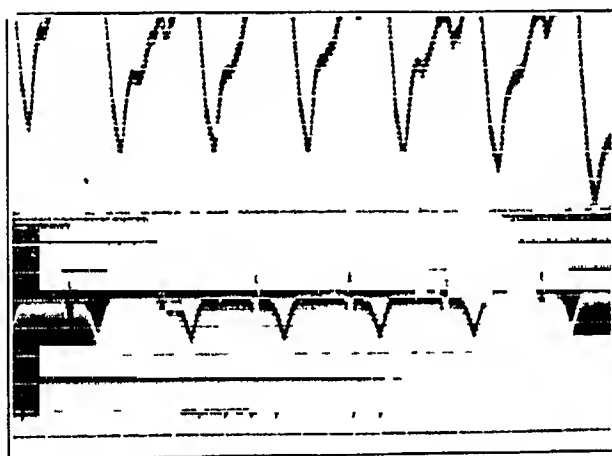


Fig 24—Subject 20, Lead 3 A-V rhythm of Type 2 which appeared spontaneously about eight minutes after atropin The ventricular complexes are abnormal, but different from those of the following figure P is not seen because it is buried in R

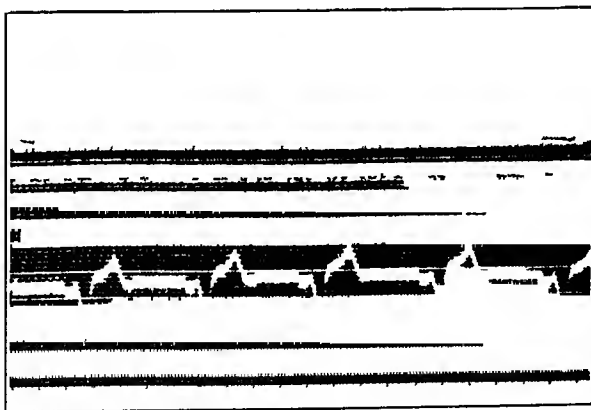


Fig 25—Subject 20, Lead 3 The rhythm before atropin P is inverted and the P-R interval is 0.10 second indicating that an A-V rhythm of Type 1 is present The ventricular complexes are abnormal because of right branch bundle block

was afterward only present after ocular pressure. The comparatively slight block which was present at the time of the last examination was probably responsible for the appearance of a typical A-V rhythm in place of the peculiar periods of auriculoventricular dissociation which were observed under atropin when the block was more marked.

Case 20 was a very complex one and will be discussed fully in another place. The patient was a young man aged 23, who suffered from attacks of paroxysmal tachycardia and who had the physical signs of mitral stenosis. The electrocardiograms showed at times the presence of an A-V rhythm of Type 1 which was complicated by a right branch bundle block. During atropin experiments an A-V rhythm of Type 2 appeared spontaneously about eight minutes after the drug was given and alternated with the normal rhythm and the A-V rhythm of Type 1 for several minutes, after which it gave place to the normal

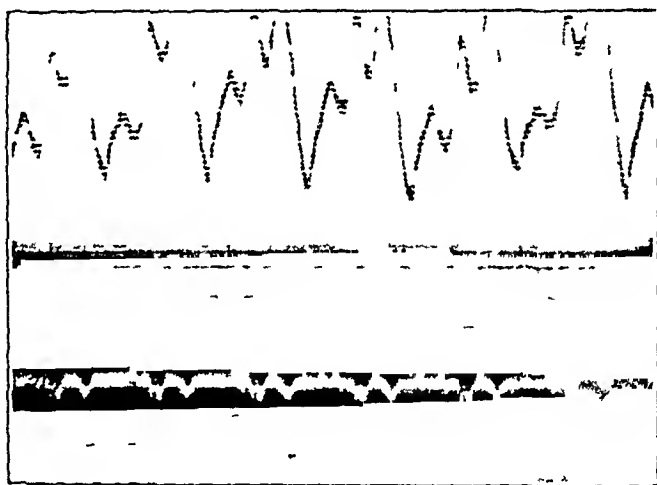


Fig 26—Subject 20, Lead 3. The normal rhythm at the height of the atropin effect. P is upright, the P-R interval is 0.17 second and the ventricular complexes are normal.

rhythm and appeared no more until the next atropin experiment was made. This rhythm is illustrated in Figure 24. It differs from the other rhythms of Type 2 described in this article in that the ventricular complexes are abnormal. The significance of these abnormal complexes will be discussed elsewhere. The heart mechanism in this case before atropin is shown in Figure 25 and the normal rhythm which appeared at the height of the atropin action is seen in Figure 26.

DISCUSSION

The special susceptibility of the heart toward A-V rhythm during the intermediate period between the hypodermic administration of atropin and the appearance of its maximum effect may be explained in the following way. Atropin increases the heart rate by paralyzing the vagus endings in the heart and thus liberating the sinus node from

the inhibitory effect ordinarily exercised by this nerve. The vagus, however, is not distributed to the sinus node alone but also to other portions of the heart and especially to the special structures at the auriculoventricular junction. Atropin paralyses these endings also, as is shown by its effect on functional heart-block, and there is every reason to suppose that this drug increases the period of the A-V node in the same way in which it increases the rate of the sinus rhythm. Because of some selective action exercised by atropin on the vagus terminations in the A-V node, however, this node is released from vagus inhibition before the sinus node. It thus happens that at a certain period of atropin action the A-V node is partially released from vagus inhibition, while the sinus node is still relatively under vagus control. At this time the period of the lower node is increased so that it approaches or exceeds the rate of the sinus rhythm. When it exceeds it, A-V rhythm appears spontaneously. When it approaches without reaching the sinus rate A-V rhythm may be produced by some method of vagus stimulation. This slows the sinus rate markedly without exerting a corresponding effect upon the A-V node.

When the atropin effect has reached its maximum, however, the sinus node is also released from vagus control and at this time its inherent rhythm is much more rapid in rate than that of the A-V node and it can not be slowed by vagus stimulation, so that A-V rhythm can no longer be produced. Vagus stimulation does not produce A-V rhythm when atropin has not been given, because, although it slows the sinus rate, it also slows the period of the A-V node sufficiently to keep it below the rate of the sinus node and hence prevents the appearance of A-V rhythm. In exceptional cases in which the period of the A-V node is pathologically rapid or less sensitive than normal to vagus stimulation, ocular pressure or forced respiration does produce A-V rhythm¹⁷ and it is not infrequent that single idioventricular beats occur in normal people as a result of the first of these procedures.

Other explanations might be offered for the production of A-V rhythm by the method described in this article. It is possible, for instance, that atropin may have some action upon the heart other than the well known paralysis of the vagi which it produces. It is also possible that ocular pressure and continued forced respiration, which were used in many of our experiments to produce A-V rhythm, may stimulate the accelerator nerves and thus tend to increase the period of the A-V node. The latter explanation would not account for the spontaneous appearance of A-V rhythm in some of the patients reported nor would it account for the fact that A-V rhythm cannot

be produced by these methods after the atropin effect has reached its maximum

THE RELATION OF A-V RHYTHM TO PALPITATION

It remains to be mentioned that three patients (Nos 8, 19 and 20) who developed A-V rhythms of Type 2 complained of marked palpitation during the abnormal rhythm. This palpitation was associated not with arterial throbbing but consisted in throbbing of the heart and a feeling of tension in the throat. It was probably due to the fact that the auricles and ventricles contracted simultaneously so that the auricles could not discharge their blood into the ventricles but forced it back into the great veins. This palpitation is entirely comparable to that felt during attacks of paroxysmal tachycardia with a positive venous pulse and the cause is the same in both instances. It seems unlikely, however, that A-V rhythm of the type here described is a frequent cause of clinical palpitation.

SUMMARY

It was found possible to produce A-V rhythm in a large proportion of young persons by vagus stimulation during the intermediate period between the hypodermic injection of atropin and the appearance of its maximum effect. In three cases, one normal and two cardiac cases, A-V rhythm appeared spontaneously under this drug. In none of the individuals of the present series who had apparently normal hearts was it possible to produce A-V rhythm before the drug had been given. This was possible, however, in two patients with cardiac disease. It was not possible to produce A-V rhythm after the atropin effect had reached its maximum in any of the subjects investigated.

We believe that the special susceptibility of the heart toward A-V rhythm during the early action of atropin is due to a selective action of this drug on the vagus terminations in the A-V node, in that it paralyzes these before it paralyzes those in the sinus node.

In two pathologic cases the A-V rhythm which appeared after atropin exhibited unusual features.

Three patients complained of marked palpitation as a result of simultaneous contraction of auricles and ventricles during A-V rhythm.

A CASE IN WHICH THE VAGUS INFLUENCED THE FORM OF THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM¹

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BUNDLE-BRANCH BLOCK

In 1910, Eppinger and Rothberger¹ published electrocardiographic tracings illustrating the effects of dividing the right and left branches of the His bundle on the ventricular complex. Eppinger and Stoerk,² later in the same year, were able to report two clinical cases of bundle-branch block in which the diagnoses, made with the aid of electrocardiograms, were confirmed at section. Since that time similar cases have been reported by a large number of authors. Carter,³ in his report of twenty-two cases, concludes that the ventricular complexes seen in cases of bundle-branch block exhibit, in contrast to normal ventricular complexes, the following characteristics. They are diphasic rather than polyphasic and are composed of (1) a primary deflection or QRS group, whose amplitude is greater than that of the normal ventricular complex and whose duration is longer, being one-tenth second or more, and (2) of a secondary deflection in the opposite direction from the first, an exaggerated T. The primary deflection usually comprises at least one-third of the entire ventricular complex and is often notched. These abnormal complexes, although produced by supraventricular stimuli, resemble very closely the electrical complexes produced by ventricular extrasystoles. When the block is in the right branch of the His bundle, as happens most often (twenty-one of Carter's twenty-two cases were of this type), the initial deflection is upward in Lead 1 and downward in Lead 3, and when the block is in the left branch the direction of the initial deflection in these leads is reversed. The fact that the right branch is so much more frequently affected than the left is probably due to its greater length.

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1 Eppinger, H., and Rothberger, J. Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel der Reizleitungssystem, *Ztsch f klin Med*, 1910, lxx, 1

2 Eppinger, H., and Stoerk, O. Zur Klinik des Elektrokardiogramms, *Ztschr f klin Med*, 1910, lxxi, 157

3 Carter, E. D. Clinical Observations on Defective Conduction in the Branches of the Auriculo-ventricular Bundle, *THE ARCHIVES INT MED*, 1914 xliii, 803

before division. In most of the cases reported the bundle-branch block has been permanent, so that it has been impossible to compare the abnormal complexes with the normal complexes of the same case. In one of Carter's patients, however, the block was transient and such a comparison could be made, and in two of Mathewson's⁴ patients transitions from the normal to the abnormal complexes were recorded electrocardiographically. In one of the patients reported by the latter, right and left bundle-branch block alternated irregularly with the normal mechanism.

EFFECT OF VAGI ON THE VENTRICULAR ELECTROCARDIOGRAM IN ANIMALS

Since the original experiments of Eppinger and Rothberger,¹ abnormal ventricular complexes similar in form to those obtained by cutting one branch of the A-V bundle have been observed under a variety of experimental conditions. They may arise in at least three ways. First, they occur when there is a block in one of the branches of the His bundle even when the ventricles are responding to supraventricular stimuli. Second, they are found when heterogenetic beats or extrasystoles arise within the ventricles below the bifurcation of the A-V bundle. Third, they may occur when homogenetic beats arise in the branches of the His bundle. There is a possibility, of course, that the latter may originate within the walls of the ventricles outside the specialized tissues, but since it seems likely that homogenetic beats rarely if ever arise outside of the specialized tissues in the auricles, it is reasonable to suppose that the same is true of the ventricles.

Abnormal ventricular complexes of this type have occasionally been associated with stimulation of the vagi in animals. If heart block be produced experimentally by mechanical destruction of the A-V bundle, the ventricular complexes of the resulting idioventricular rhythm are always of the normal form. When, however, A-V dissociation is produced in animals by strong stimulation of the vagi, the ventricular complexes are often abnormal and typically diphasic. This was pointed out by Einthoven⁵ as early as 1906 and similar observations have been made by Kahn⁶ and by Kraus and Nicolai.⁷ In such cases the ventricular contractions are of the homogenetic type since they always occur rhythmically and at a slow rate. We must assume,

4 Mathewson, G. D. Lesions of the Branches of the A-V Bundle, *Heart*, 1912-1913, iv, 385.

5 Einthoven, W. Le Telecardiogramme, *Arch. internat. de physiol.*, 1906, iv, 132.

6 Kahn, R. H. Beiträge zur Kenntnis des Elektrokardiogramms, *Arch. f. d. ges. Physiol.*, 1909, cxxvi, 197.

7 Kraus, F., and Nicolai, G. F. Das Elektrokardiogramm des gesunden und kranken Menschen, Leipzig, 1910.

therefore, that the vagus stimulation influenced the idioventricular electrocardiogram in these instances either because it altered the location of the idioventricular pace-maker or produced bundle-branch block

Whether or not vagus stimulation may alter the form of the ventricular complexes when the ventricles are responding to supraventricular stimuli has been much discussed. In 1909, Hering⁸ recorded abnormal ventricular complexes during vagus stimulation in a dog, and each ventricular beat was preceded by an auricular beat, as shown by the electrocardiogram and the suspension curve. Hering was of the opinion that these ventricular beats were supraventricular in origin, an interpretation which has been questioned by others.⁹ If Hering's view is the correct one, we must assume a bundle-branch block to account for the form of the ventricular complexes. A similar assumption would be necessary to explain the abnormal ventricular complexes obtained by Kraus and Nicolai⁷ by stimulating the auricles during complete vagus inhibition.

Rothberger and Winterberg¹⁰ found that stimulation of either accelerator nerve during vagus inhibition almost always gave rise to rhythmic and typically diphasic ventricular complexes. In some of their figures¹⁰ (Fig 1c p 466) each abnormal ventricular complex is preceded by an auricular contraction. It seems to us possible that in these instances the abnormal ventricular beats were responses to supraventricular stimuli. If this be true we would again be dealing with an abnormal spread of a supraventricular stimulus over the ventricles as a result of nervous influences. The effect of vagus stimulation was complicated in these experiments, however, by the effect of accelerator stimulation, and, moreover, the type of ventricular complex depended on which accelerator was stimulated, so that conclusions as to the relationship of the vagi to the abnormal complexes are difficult to draw. A summary of the experimental evidence shows that although it is possible that vagus stimulation produced bundle-branch block in animals in certain instances, unquestionable examples of this phenomenon are lacking.

8 Hering, H. E. Experimentelle Studien am Säugetieren über das Elektrokardiogramm, *Arch f d ges Physiol*, 1909, cxxvii, 155.

9 Kahn, R. H. Das Elektrokardiogramm, *Ergebn d Physiol*, 1914, xiv, 1. Samojloff, A. Weitere Beiträge zur Elektrophysiologie des Herzens, *Arch f d ges Physiol*, 1910, cxxxv, 417. Rothberger, J., and Winterberg, H. Ueber die Beziehung der Herznerven zur Form des Elektrokardiogramms, *Arch f d ges Physiol*, 1910, cxxxv, 506.

10 Rothberger, J., and Winterberg, H. Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachycardie durch Acceleransreizung, *Arch f d ges Physiol*, 1911, cxli, 461.

So far as we know, no clinical case has as yet been reported in which stimulation of the vagus produced diphasic ventricular complexes. In the following case vagus stimulation produced such complexes although the ventricles were responding to supraventricular stimuli. The case also presents other unusual features. The history and examination of the patient have been recorded in another place¹¹ (Case 2)

BUNDLE-BRANCH BLOCK PRODUCED BY VAGUS STIMULATION

This patient showed at times no less than four separate and distinct rhythms. Rhythm 1, the normal rhythm, is illustrated in Figures 1, 2 and 3. The electrocardiograms have a normal outline in Leads 1 and 2, while in Lead 3 the QRS group of the ventricular complex is one of those bizarre forms occasionally recorded in this lead even in people with normal hearts¹². T is partially inverted in Lead 3. The P-R interval of the normal rhythm is about 0.17 second and the a-c interval about 0.20 second.

The second rhythm observed, which may be called Rhythm 2, is illustrated in Figures 4, 5 and 6. Both the auricular and the ventricular complexes are abnormal. P is upright in Lead 1 and inverted in Leads 2 and 3. The P-R interval is reduced to about 0.10 second and the a-c interval to about 0.15 second. The reduction of the As-Vs interval with the inversion of P in Leads 2 and 3 indicates that the site of origin of this rhythm was in the neighborhood of the A-V node. The fact that the P-R interval is only slightly reduced means that the pace-maker was in the upper part of this region.

The ventricular complexes of Rhythm 2 are abnormal in all leads. In contrast to those of the normal rhythm they exhibit the following characteristics: they are typically diphasic rather than polyphasic. The initial deflection is of greater amplitude and of longer duration, its duration being 0.10 second or more. The final deflection extends in the opposite direction from the initial deflection in all leads and is exaggerated especially in Leads 2 and 3. These characteristics indicate that the abnormality of the ventricular complexes of Rhythm 2 is due to bundle-branch block. The fact that the initial deflection is upright in Lead 1 and inverted in Lead 3 indicates that the right branch of the His bundle is the one affected. Rhythm 2 may therefore be described as an atrioventricular rhythm with right bundle-branch block.

The relationship between the normal rhythm and Rhythm 2 was as follows. During the first few days that the patient was under

11 Wilson, Frank N. Three Cases Showing Changes in the Location of the Cardiac Pace-Maker, Associated with Respiration, *THE ARCHIVES INT. MED.*, 1915, xvi, 86.

12 Lewis, T. *Clinical Electrocardiography*, London, 1912.

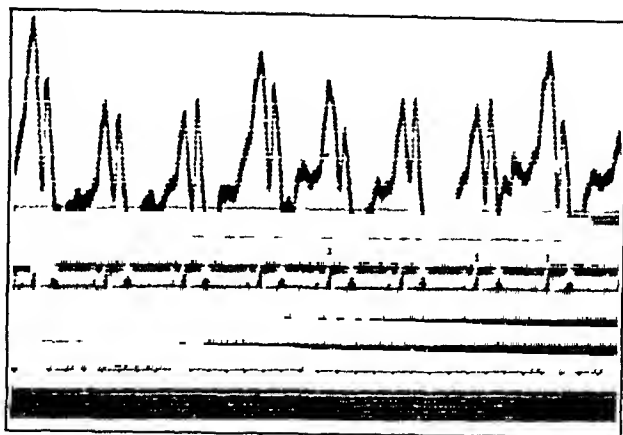


Fig 1—In this, as in the figures which follow, an ordinate of 1 cm is equal to 1 millivolt Rhythm 1, Lead 1 P-R interval, 0.17 second, a-c interval, 0.20 second Duration of QRS group, 0.08 second Heart rate 75

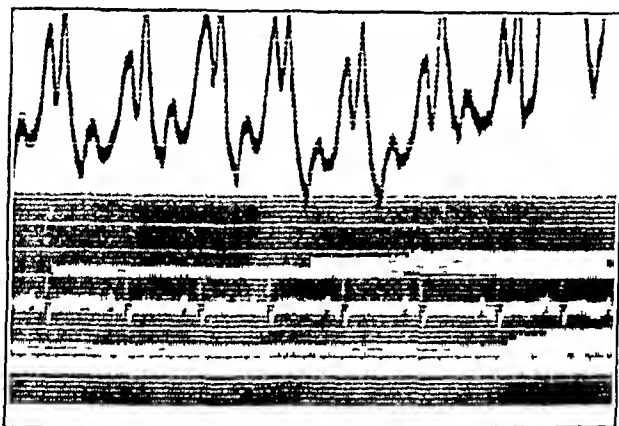


Fig 2—Rhythm 1, Lead 2 The P-R and a-c intervals are the same as in the previous figure Duration of QRS group, 0.08 second Heart rate 75

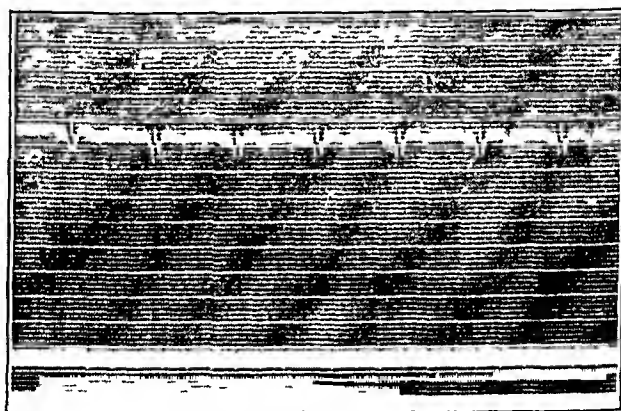


Fig 3—Rhythm 1, Lead 3 The P-R interval is the same as in Figure 1 Duration of QRS group, 0.10 second The QRS group is bizarre and T is partially inverted

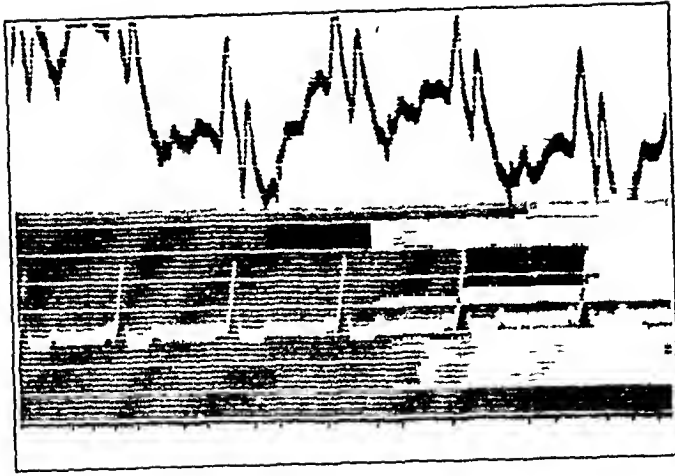


Fig 4—Rhythm 2, Lead 1 P-R interval, 0.10 second, a-c interval 0.15 second Duration of QRS group, 0.10 second The amplitude of R' is greater than that of R in Figure 1 T is inverted P is upright Heart rate 66

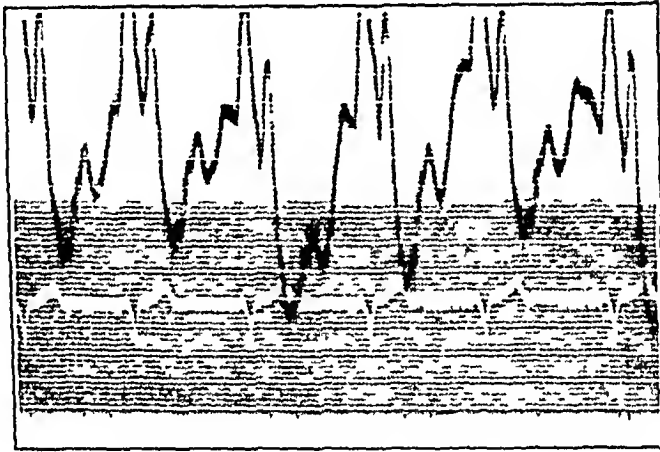


Fig 5—Rhythm 2, Lead 2 The P-R and a-c intervals are the same as in Figure 4 Duration of QRS group, 0.10 second The ventricular complex is diphasic and T is exaggerated P is inverted Heart rate 62

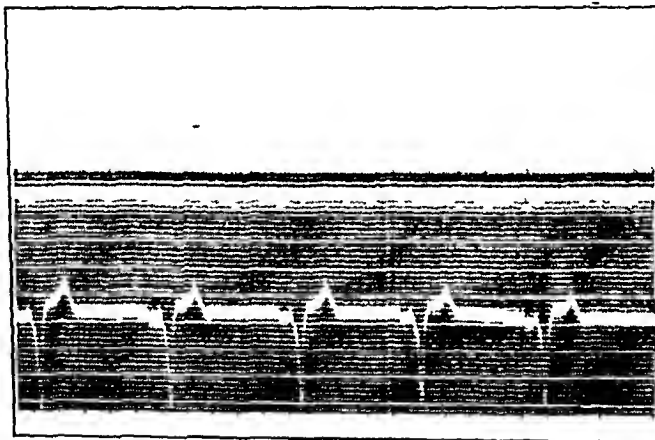


Fig 6—Rhythm 2, Lead 3 The P-R interval is the same as in Figure 4 Duration of QRS group, 0.13 second The amplitude of the initial deflection is greater than that of the initial deflection of the ventricular complexes in Figure 3 T is exaggerated P is inverted Heart rate 62

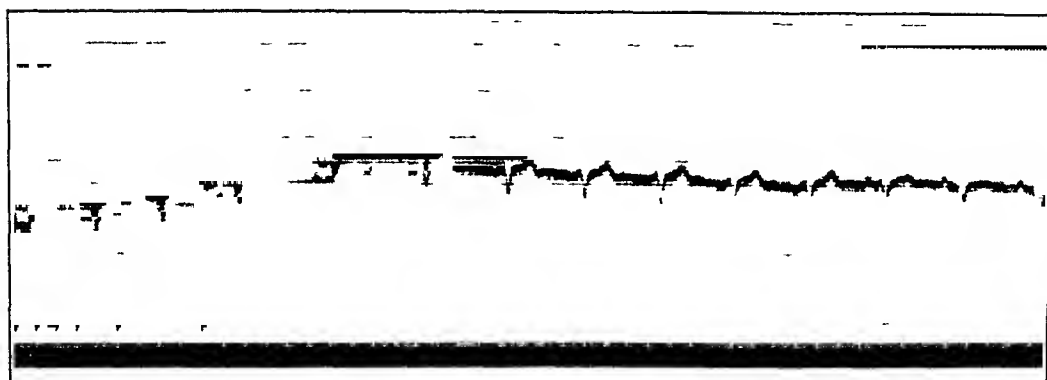


Fig 7—Lead 2 Rhythm 1 converted into Rhythm 2 by moderately deep respiration. Note the transitional ventricular complex at the end of the abnormal rhythm.

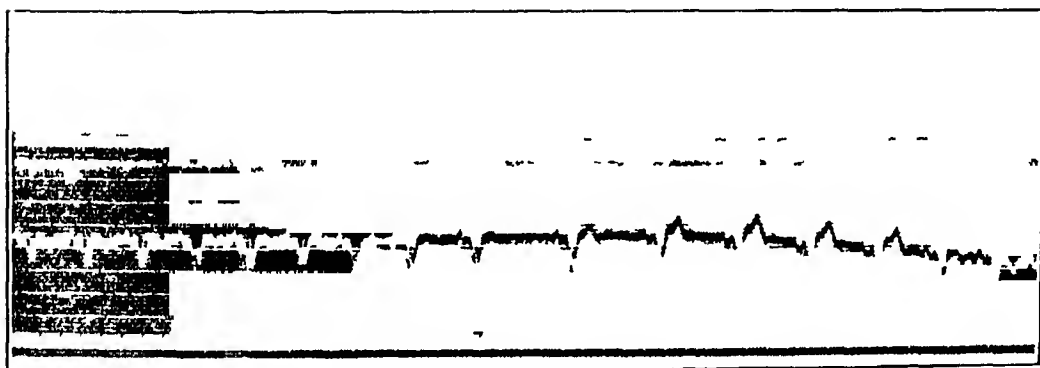


Fig 8—Lead 3 Rhythm 1 converted into Rhythm 2 by deep respiration. At the beginning of the abnormal rhythm the change in the form of P is sudden while the change in the form of the ventricular complex is gradual.

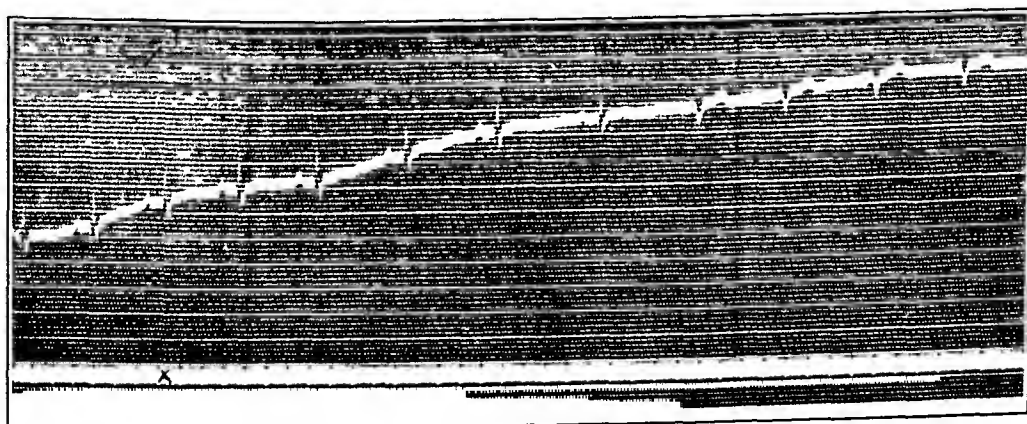


Fig 9—Lead 2, Rhythm 1 converted into Rhythm 2 by pressure on the right vagus. Pressure was begun at x and continued until the abnormal rhythm appeared.

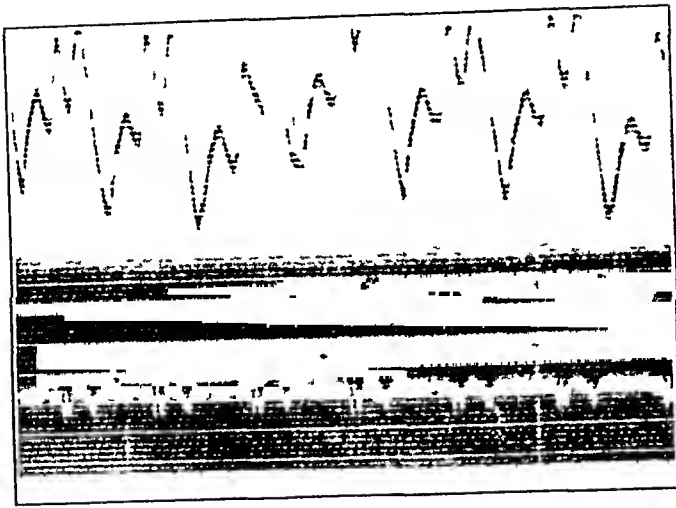


Fig 10—Rhythm 1, Lead 3 Taken at the end of an atropin experiment
Rhythm 2 was constantly present before the atropin was given

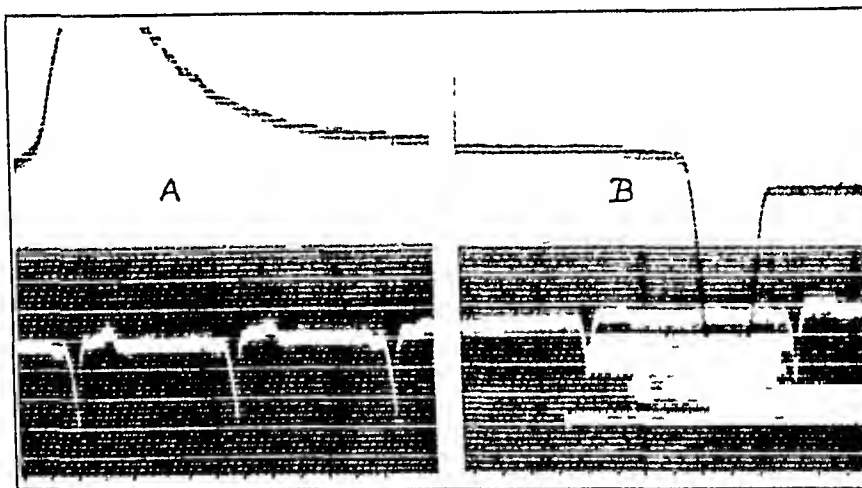


Fig 11—Rhythm 2, Lead 3 Rhythm 2 slowed by right vagus pressure,
A, beginning, and B end of a period of right vagus pressure lasting eleven
seconds

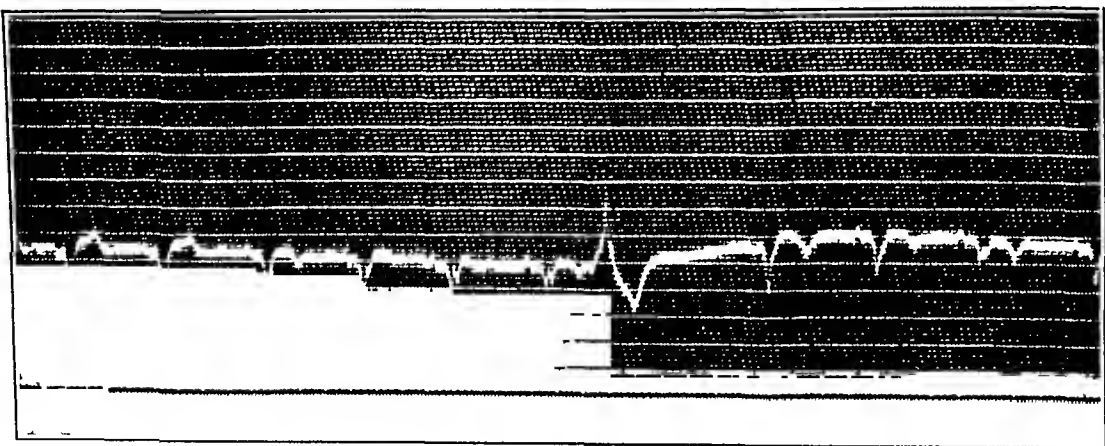


Fig 12—Lead 3 The first part of the figure shows a gradual transition
from Rhythm 2 to Rhythm 1 This transition took place spontaneously The
P complex of the third cycle is transitional between those that precede and
those that follow it A ventricular extrasystole occurs

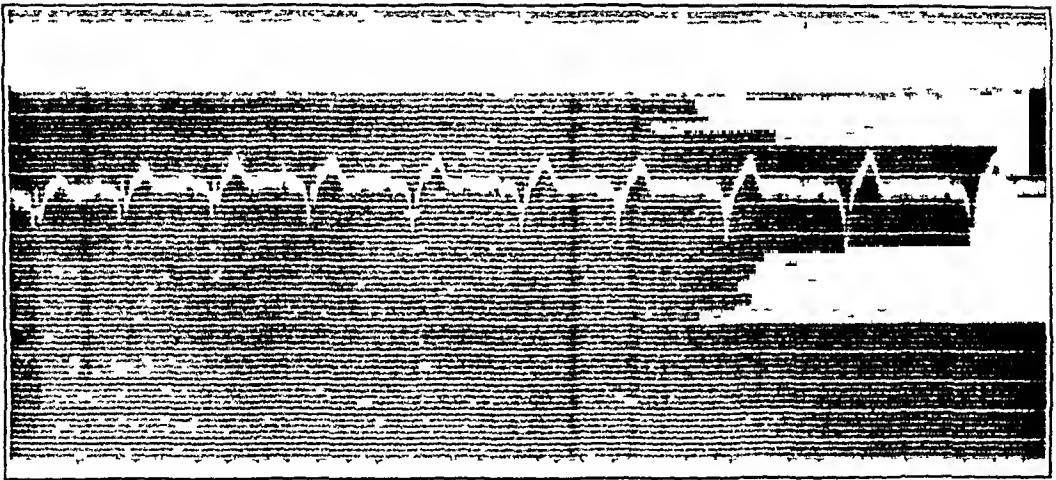


Fig 13—Lead 3 P is upright throughout the figure and the P-R interval is that of Rhythm 1. There is a gradual transition from complexes of the normal type to those characteristic of right branch block. Note the disappearance of the upright spike of the normal ventricular complex during the transition.

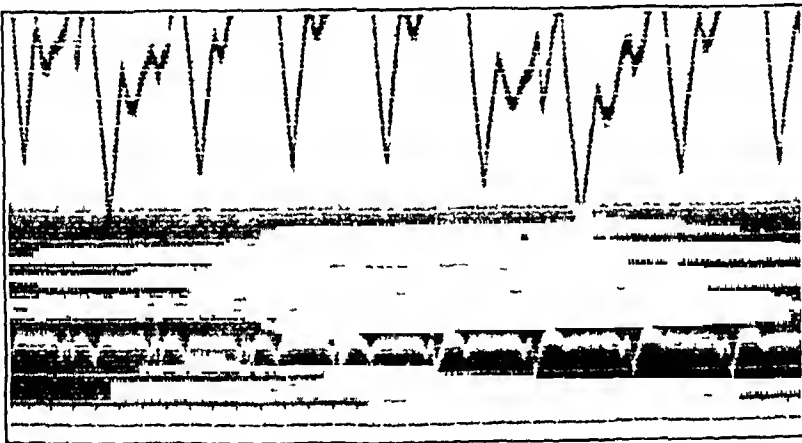


Fig 14—Lead 3 P is inverted and the P-R interval is reduced. The first four ventricular complexes are of the normal type. The last four ventricular complexes are diphasic and are of the type associated with Rhythm 2 except that their amplitude is much less. This curve was taken during an atropin experiment. The last four ventricular complexes probably represent incomplete branch block.

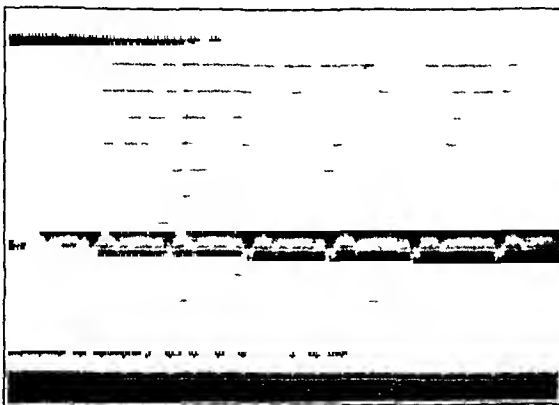


Fig 15—Lead 3 The inverted auricular complexes of Rhythm 2 are associated with the ventricular complexes of Rhythm 1.

observation, the normal rhythm was the one usually present. At this time Rhythm 2 could be produced almost at will by having the patient take a deep breath (Figs 7 and 8). The abnormal rhythm appeared shortly after the beginning of expiratory slowing and after persisting for a number of beats disappeared as the heart rate quickened. The normal rhythm could also be converted into the abnormal rhythm by pressure upon the vagus nerves (Fig 9). No difference between the two vagi was noted. Although, when the first electrocardiograms were taken, Rhythm 2 disappeared shortly after it was produced by deep breathing or vagal pressure, as time went on it showed a greater and greater tendency to persist, and at the end of the first week of the examination it was the rhythm usually present. At this time the normal rhythm could be produced by having the patient take a rapid succession of deep breaths. It was also possible to convert Rhythm 2 into the normal rhythm by the subcutaneous administration of 1/50 grain of atropin (Fig 10) and this was done on five different occasions. After the normal rhythm had been produced by atropin it was impossible to cause Rhythm 2 to return by forced respiration or by any other means used to produce it before it appeared spontaneously.

Rhythm 2 could be slowed considerably by vagus stimulation (Fig 11) the right vagus being somewhat more effective than the left. This shows that in this patient the upper portion of the junctional tissues was under vagus control.

To sum up, the normal rhythm when spontaneously present could be converted into an atrioventricular rhythm with right branch-bundle block by indirect or direct stimulation of the vagus nerves, and the abnormal rhythm when spontaneously present could be converted into the normal rhythm by the administration of atropin in doses sufficient to paralyze the vagi. This group of facts can lead to but one conclusion and that is that the vagi were partially responsible both for the change in the location of the pace-maker and for the abnormality of the ventricular complexes. The relationship of these nerves to the former has been discussed elsewhere¹¹ (Case 2).

Before discussing the effect of the vagus on the form of the ventricular complexes, it is necessary to examine the relationship between the A-V rhythm and the bundle-branch block. The fact that both are so constantly associated in the present case might lead one to suspect that the abnormal location of the pace-maker was entirely responsible for the abnormality of the ventricular complexes. It is difficult to see how this could be possible, for as has been pointed out above, the pace-maker must have been situated high up in the junctional tissues above the division of the His bundle. Even in complete heart block, when the pace-maker is much lower and nearer to the bifurcation of the A-V

bundle, the ventricular complexes are normal. Furthermore, in the present case, although the change in the location of the pace-maker was an abrupt one the change in the form of the ventricular electrocardiogram was often very gradual (Fig 8). Transitional P waves were sometimes seen at the onset or offset of the A-V rhythm (Fig 12) but these were due not to a gradual change in the location of the pace-maker but to interference between two contraction waves, one beginning at the sinus and the other at the A-V node¹¹. That the abnormality of the ventricular complexes did not depend on the presence of A-V rhythm is also demonstrated by the fact that transitions between the normal and the abnormal complexes sometimes occurred without the pace-maker leaving the sinus node (Fig 13). At other times, on the other hand, an A-V rhythm of the same type as that of Rhythm 2 was associated with ventricular complexes of the

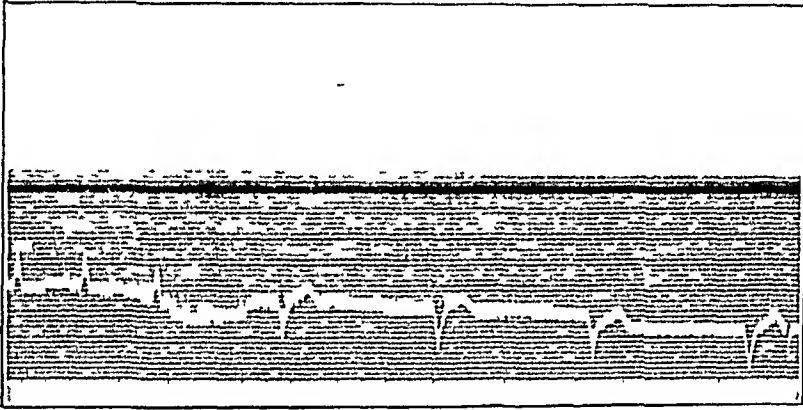


Fig 16—Lead 1. This curve illustrates the production of diphasic ventricular complexes in a second patient (see text). P cannot be seen during the abnormal rhythm.

normal type (Figs 14 and 15). It would seem therefore that the bundle-branch block of Rhythm 2 did not depend on the abnormal site of impulse formation but that both were coordinated effects of vagus influence.

It is of course improbable that the bundle-branch block was due to vagus influence alone for it is rarely possible to produce diphasic ventricular complexes by vagus stimulation. We have carried out this procedure in a considerable number of patients and we have been able to produce such complexes in but one other instance (Fig 16). The unsatisfactory character of the records obtained in that instance made it impossible to tell whether or not the ventricles were responding to supraventricular stimuli. It is probable therefore that in the previous patient, conduction through the right branch of the A-V bundle was already impaired and that this rendered it especially susceptible to vagus influence.

INCOMPLETE BUNDLE-BRANCH BLOCK

The characteristics of the abnormal ventricular complexes produced by the complete interruption of conduction through one branch of the A-V bundle are fairly well known both from experimental and clinical observations. Very little is known, however, about the ventricular complexes of incomplete block in one of the branches of the A-V bundle. For this reason, gradual transitions between normal ventricular complexes and those of bundle-branch block are of par-

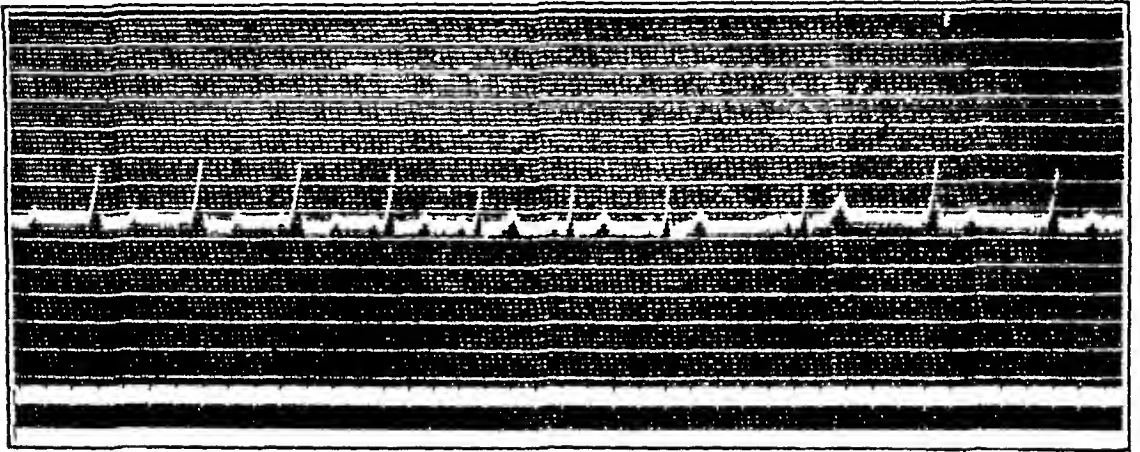


Fig 17—Lead 1 A spontaneous transition from Rhythm 2 to Rhythm 1 and the return to Rhythm 2. The transitions are sudden.

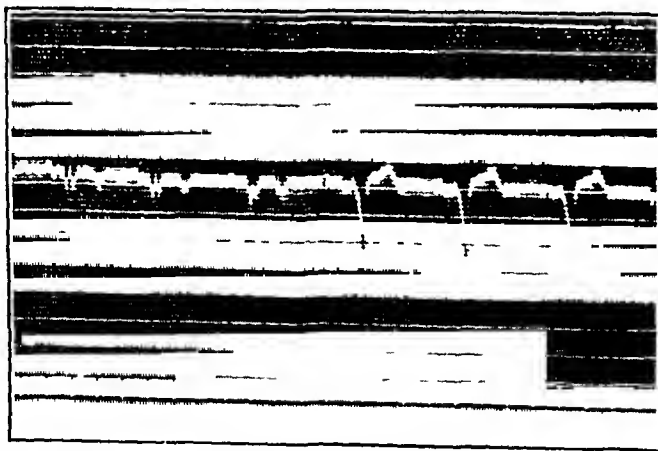


Fig 18—Lead 3 A sudden transition from Rhythm 1 to Rhythm 2.

ticular interest for presumably they represent varying degrees of partial bundle-branch block and their analysis may aid in the recognition of this condition when transitions are absent. In the present case, some of the transitions from the normal to the abnormal complexes were sudden (Figs 17 and 18), but as a rule they were gradual. For the purpose of determining the characteristics of the ventricular complexes of partial bundle-branch block spontaneous transitions should be chosen

in order to eliminate the effects of the respiratory changes in the position of the heart on the ventricular complex. Such spontaneous transitions from normal to abnormal and from abnormal to normal complexes are shown in Figures 12 and 13. From the analysis of a large number of such transitions it was found that changes in the QRS group and in T usually appeared simultaneously. The most constant feature of the transitional complexes was their diphasic character, which was usually evident even in those nearest the normal complexes, and this change is probably present in the lightest grade of block. On the other side, the transitional complexes differed from the fully developed abnormal complexes principally in their lesser amplitude. As one proceeds from the abnormal complexes to those typical of complete branch-bundle block the amplitudes of the QRS group and of T gradually increase, and as these two deflections are in opposite directions the diphasic character of the complexes is gradually accentuated (Figs 8 and 13). Although an increase in the duration of the initial deflection usually appeared with the first of the abnormal complexes it was usually much less striking than their diphasic character. The disappearance of the upright spike of the QRS group of the normal ventricular complex in Lead 3 during the transitions is interesting (Figs 8 and 13).

VENTRICULAR COMPLEXES SUGGESTING LEFT BUNDLE-BRANCH
BLOCK AT THE BEGINNING OF ATROPIN EXPERIMENTS AND
DURING PAROXYSMS OF TACHYCARDIA

The effect of atropin on Rhythm 2 was complicated by a new rhythm which usually appeared about eight minutes after the injection of 1/50 grain of atropin sulphate and recurred with frequent transitions to the normal rhythm for from three to five minutes. This third rhythm is illustrated in Figures 19 (Lead 1) and in 20 (Lead 3). Although no P waves are seen in the electrocardiogram, it is evident from the tall venous waves which occurred during this rhythm (Fig 21) that auricles and ventricles contracted simultaneously. This indicates that the site of origin of Rhythm 3 was in the lower junctional tissues. The change in the location of the pace-maker from the upper (Rhythm 2) to the lower (Rhythm 3) junctional tissues after atropin is probably analogous to the appearance of A-V rhythm in normal individuals under similar conditions¹³. The transitions between Rhythm 1 and Rhythm 3 differed from those between Rhythm 1 and Rhythm 2 in that they were usually sudden (Figs 19, 20 and 22). Ventricular complexes which may be regarded as transitional in form

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between the ventricular complexes of the normal rhythm and those of Rhythm 3 were frequently recorded, however, and these usually occurred during a period just preceding the appearance of Rhythm 3. These transitional complexes (Fig 23) appeared only after atropin and were not associated with any change in the location of the pacemaker as is shown by the length of the P-R interval and the form of the P waves which precede them (Fig 23). It seems likely, therefore, that in Rhythm 3 as in Rhythm 2 the abnormality of the ventricular complexes did not depend on the abnormal site of impulse formation.

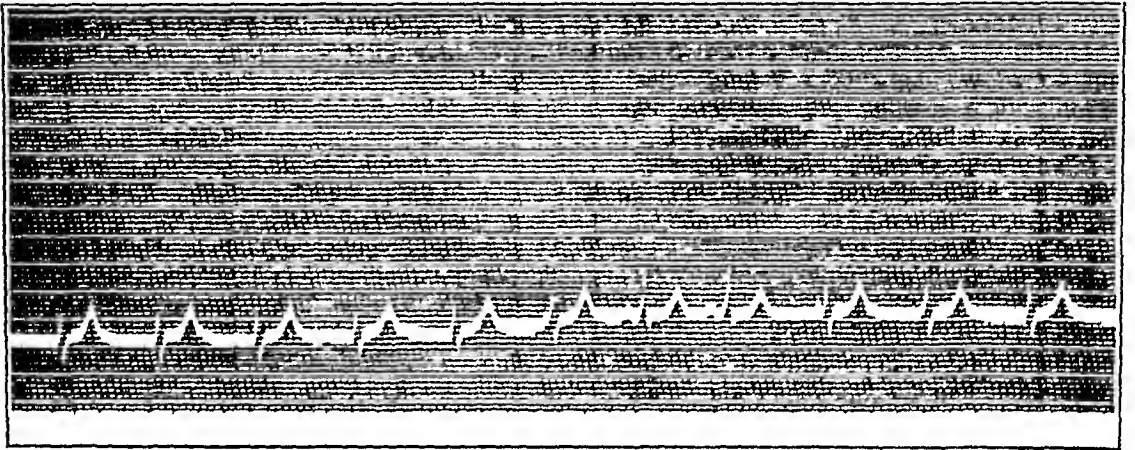


Fig 19—Rhythm 3, Lead 1. The ventricular complexes are not diphasic but T is exaggerated. A transition from Rhythm 3 to Rhythm 1 occurs. P cannot be identified during Rhythm 3.

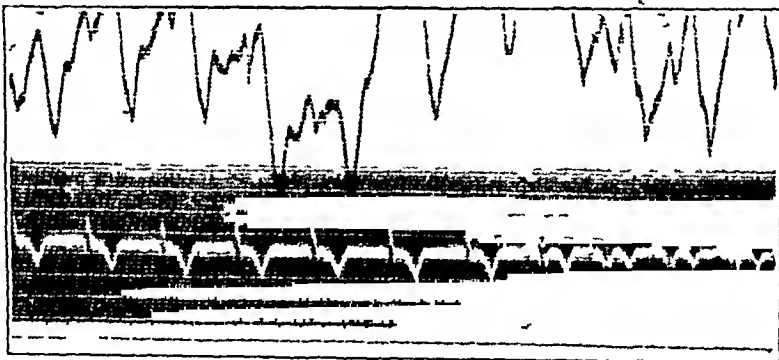


Fig 20—Lead 3. A transition from Rhythm 3 to Rhythm 1 is shown. P is not visible during Rhythm 3.

Transitions between a sinus rhythm and Rhythm 3 are illustrated in Figures 19 and 22. The P wave gradually approaches the ventricular complex and finally disappears within it. The reverse process occurs when the abnormal gives place to the normal rhythm (Figs 20 and 22). The fact that the P waves remain normal during the transitions indicates that the auricular contractions which they represent were responses to the sinus node. The shortening of the P-R interval indicates, therefore, that a lower center has escaped and that

the ventricles are responding to this center. After several heart cycles the higher rate of this lower center enabled it to replace the sinus node as pace-maker for the auricles also. The reverse process took place when the inherent rate of the sinus became more rapid than that of the ectopic center. When transitions occurred between Rhythm 2 and Rhythm 3 a similar phenomenon took place. The inverted P of Rhythm 2 gradually approached and disappeared into the ventricular

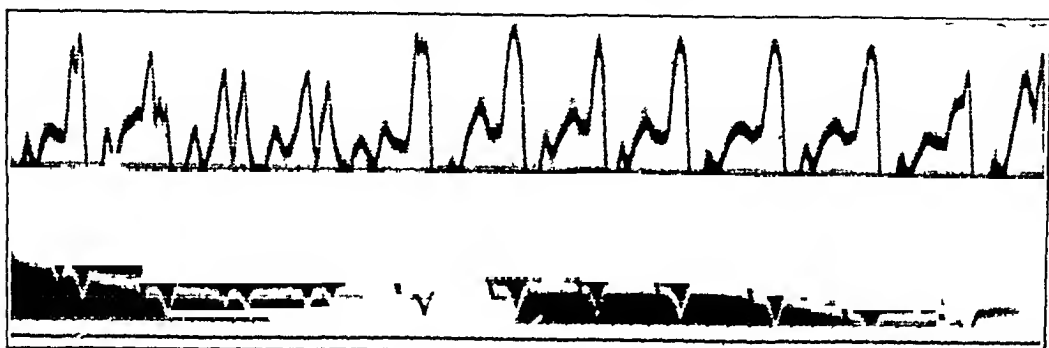


Fig 21—Lead 3. A transition from Rhythm 1 to Rhythm 3 occurs in the last part of the figure. The venous pulse during Rhythm 3 is dominated by a tall wave such as is usually seen when auricles and ventricles contract simultaneously. This wave is no broader than the *a* wave which occurs during the normal rhythm (Cycles 3 and 4). Note that even when P only just emerges from the ventricular complex in the second cycle from the right hand side of the figure *a* and *c* are separately indicated in the venous pulse.

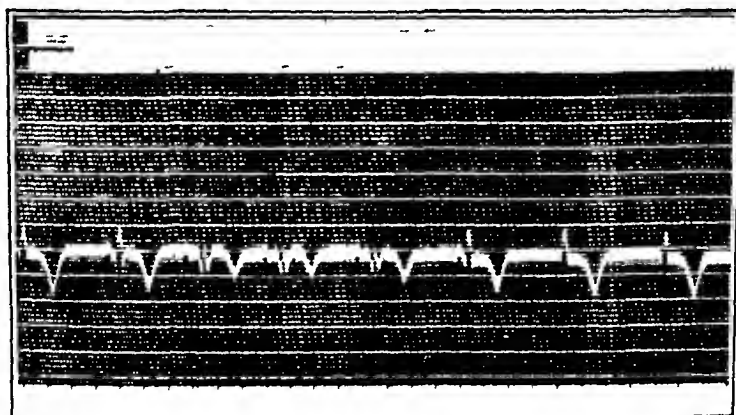


Fig 22—Lead 3. A transition from Rhythm 3 to sinus rhythm occurs and also a transition in the reverse direction. Notice that P moves out of the ventricular complex at the end of Rhythm 3 and reenters the ventricular complex when Rhythm 3 reappears.

complex. The period of transition lasted for only one or two complexes, however, because of the close proximity of the two opposing centers (Fig 24). The fact that P never emerged between R and T indicates that the impulses from the center which was responsible for Rhythm 3 must have reached the auricles at some time during the R wave, or in other words that these impulses arose from the region of

the A-V node itself. The tall venous waves of Figure 21 also indicate that during Rhythm 3 auricular systole fell during the first portion of ventricular contraction.

The ventricular complexes of Rhythm 3 are distinctly abnormal. In Lead 3 (Fig 24) they are typically diphasic. The duration of the initial deflection is not distinctly lengthened but its amplitude is increased and T is exaggerated. In Lead 1 (Fig 19) the ventricular

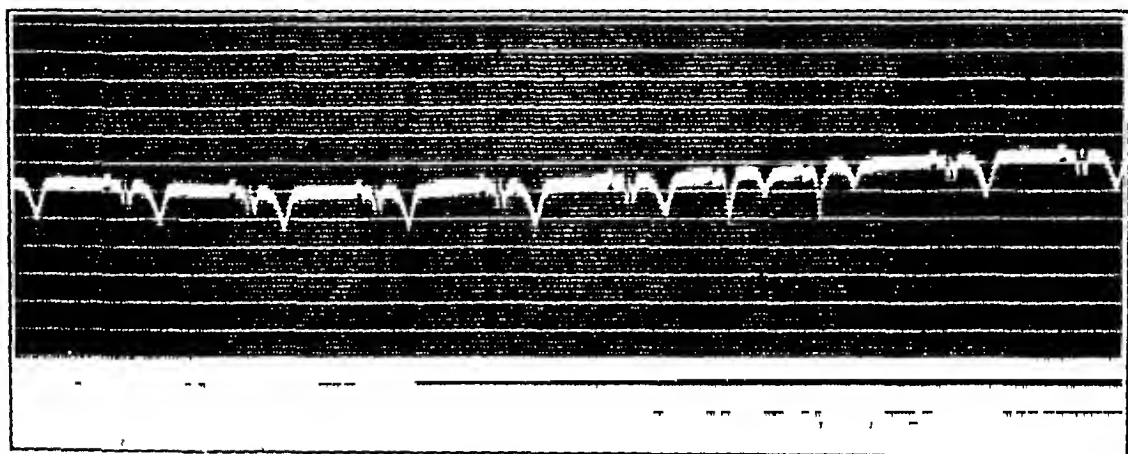


Fig 23 Lead 3 Taken during an atropin experiment. The ventricular complexes of the first part of the figure are transitional between those of the normal type and those seen in Rhythm 3. Two ventricular complexes transitional in form between the ventricular complexes in the first part of this figure and the ventricular complexes of Rhythm 2 occur in the latter part of the curve.

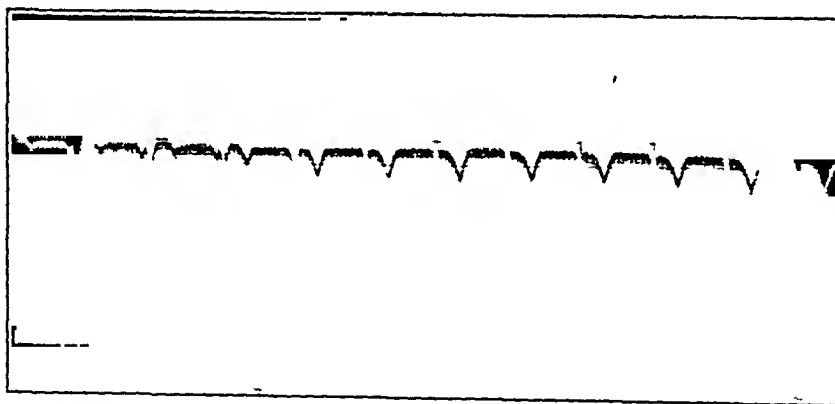


Fig 24—Lead 3. A transition from Rhythm 2 to Rhythm 3 occurs. The inverted P wave enters the ventricular complex at the beginning of Rhythm 3. The period of transition is short.

complexes are not diphasic. When compared with the normal, however, R is shorter while S and T are exaggerated. Before discussing the question of the significance of these abnormal complexes let us examine a fourth rhythm observed in this patient.

This patient had at times paroxysms of tachycardia which always began and ended suddenly. During the six weeks that he was under observation two such attacks were recorded. The rhythm present at

these times is illustrated in Figures 25, 26 and 27. Both attacks were stopped by Valsalva experiments and the end of one of them is shown in Figure 28. In this figure it will be seen that the abnormal rhythm ceased abruptly and after a long postparoxysmal pause the sinus rhythm returned. The rate of the heart during the paroxysm was about 170. In contrast to most patients who are subject to attacks of paroxysmal tachycardia our patient exhibited very few single extrasystoles, only two (Figs 12 and 28) were recorded in a large number of tracings and these being of the ventricular type bore no relationship to the attacks of tachycardia.

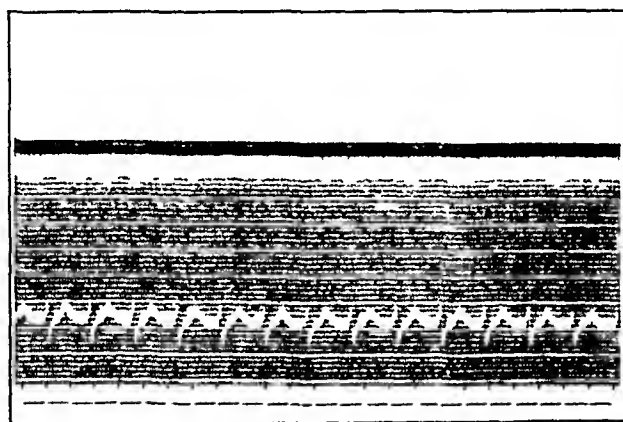


Fig 25—Rhythm 4, Lead 1. The ventricular complexes are like those in Figure 20. P is not seen.

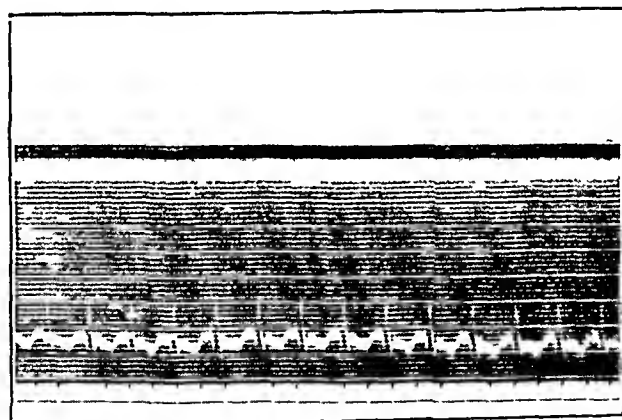


Fig 26—Rhythm 4, Lead 2. The ventricular complexes are diphasic. P is not seen. The heart rate is 170.

The electrocardiograms taken during the attacks show no definite P waves and except for the difference in heart rate resemble very closely those obtained during Rhythm 3. The venous pulse is of the positive type usually seen in paroxysmal tachycardia (Fig 27). Such a phenomenon may be due either to the fact that the auricular contractions fall on the ventricular contractions of the previous heart cycle

or it may be due to the fact that both chambers are stimulated simultaneously from a pace-maker in the junctional tissues. There are two reasons for thinking that the latter explanation is the correct one in the present case. The first is the marked similarity between the electrocardiograms of Rhythms 3 and 4. This close resemblance between the electrocardiograms of the two rhythms makes it seem likely that they originated at the same point. The second reason for thinking

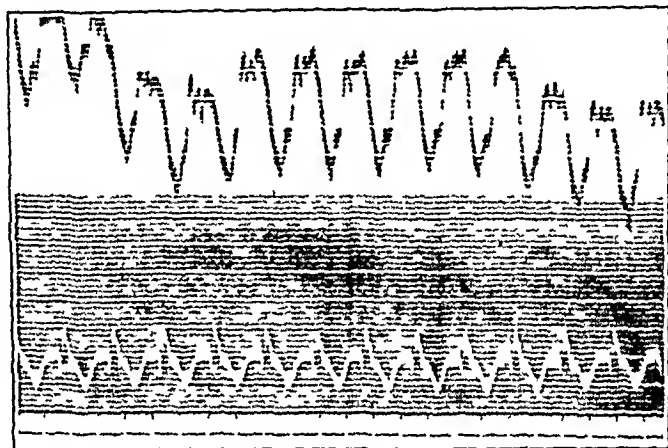


Fig 27—Rhythm 4, Lead 3. The ventricular complexes are typically diphasic and like those of Rhythm 3 in this lead. P is not seen.

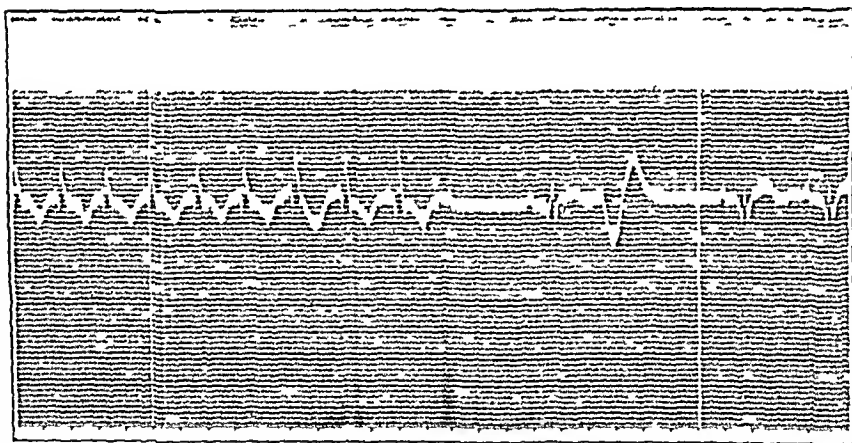


Fig 28—The end of an attack of paroxysmal tachycardia is shown. There is a long postparoxysmal pause followed by a normal contraction and then an extrasystole. The last ventricular complex of the paroxysm does not differ from the preceding ones.

that Rhythm 4 arose in the junctional tissues is that the last ventricular complex of the paroxysm does not differ from the rest (Fig 28). This is not the case when auricular contraction falls on the ventricular contraction of the previous heart cycle, for when this occurs the last ventricular complex of the paroxysm, unlike the others is not modified by a simultaneous P. Paroxysmal tachycardia originating within the

junctional tissues is comparatively rare. Cases have been studied electrocardiographically by Lewis¹⁴ and by Cohn¹⁵

The abnormal ventricular complexes of Rhythms 3 and 4 may have been due to an abnormal spread of the contraction wave over the ventricles because of a block in the conduction system. These complexes strongly suggest a block in the left branch of the His bundle but they are not perfectly typical. This discrepancy may be explained by assuming that the block was a partial one affecting the left branch itself or a complete one affecting one of the divisions of this structure.

Rothberger and Winterberg⁹ have shown that the accelerator nerves when stimulated separately may profoundly change the contour of the ventricular complexes even when these are responses to supra-ventricular stimuli. These investigators have obtained complexes of somewhat the same outline as those of Rhythms 3 and 4 by stimulation of the accelerator but we regard it as improbable that the abnormal complexes of these rhythms were due to abnormal activity of this nerve.

In the present case therefore the ventricular complexes were at times normal, at times typical of right bundle-branch block, and at still other times suggestive of left bundle-branch block. It does not seem to us that a complete explanation can be offered for all the changes observed but it should be pointed out that a similar condition of affairs has been observed both in man and in experimental animals. We have already referred to the clinical case described by Mathewson⁴ in which an irregular alternation of ventricular complexes of right and left branch block with complexes of the normal type occurred. A similar heart mechanism can be produced in animals by ligation of the septal artery (Kahn⁹). The variations in the ventricular complexes in the present case differ from similar variations previously observed, however, in that they were, in a great measure at least, produced by changes in vagus influence.

SUMMARY

The case here reported showed at different times four distinct rhythms and at least three types of ventricular complexes.

In the first rhythm the ventricular complexes were normal and the pace-maker was in the normal location.

In the second rhythm the ventricular complexes were characteristic of a block in the right branch of the His bundle. These abnormal

¹⁴ Lewis, T. Auricular Fibrillation and its Relationship to Clinical Irregularity of the Heart, *Heart*, 1909-1910, 1, 306, Paroxysmal Tachycardia, Accompanied by the Ventricular Form of Venous Pulse, *Heart*, 1910-1911, 11, 127.

¹⁵ Cohn, A. E. A Case of Paroxysmal Tachycardia, *Heart*, 1910-1911, 11, 170.

ventricular complexes were usually but not always associated with an atrioventricular rhythm originating in the upper levels of the junctional tissues. Both the A-V rhythm and the abnormal ventricular complexes could be produced by vagus stimulation and when spontaneously present could be abolished in favor of the normal rhythm by the administration of atropin.

Ventricular complexes, transitional in form between the normal complexes and the abnormal complexes mentioned above are discussed.

Rhythm 3 appeared during the early stages of atropin action and at no other time. The ventricular complexes of this rhythm were abnormal and suggested a block in the left branch of the His bundle. The pace-maker was situated in the region of the A-V node. Ventricular complexes transitional in form between those of the normal rhythm and those of Rhythm 3, occurred, however, while the pace-maker was situated at the sinus node. It is probable therefore that the abnormality of the ventricular complexes of Rhythm 3 did not depend on the abnormal site of origin of this rhythm.

Rhythm 4 was a paroxysmal tachycardia which originated at the same point as Rhythm 3 and which was associated with the same type of ventricular complex.

The various changes in the mechanisms of the heart beat observed in this case occurred, in a great measure at least, in response to changes in vagus control.

Although the changes in the form of the ventricular complex were usually associated with a change in the location of the site of impulse formation, this was not invariably the case, so that it is likely that both these changes were coordinated effects of variations in vagus influence.

OIDIOMYCOSIS IN CALIFORNIA, WITH ESPECIAL REFERENCE TO COCCIDIOIDAL GRANULOMA

INCLUDING NINE NEW CASES OF COCCIDIOIDAL GRANULOMA AND ONE OF SYSTEMIC BLASTOMYCOSIS¹

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A discussion of that form of oidiomycosis which is known as coccidioidal granuloma would seem to be appropriate at this congress, since it is a disease which is apparently confined to the American continents. The first reported case was observed by Posadas¹ in Buenos Aires, and was described by that author and by Wernike². The remaining thirty-nine cases have been observed in North America, the majority in California, and of the latter the greater number seem to have acquired the disease in the San Joaquin Valley. The first case which was recognized in California was reported by Rixford³ in 1894, and, together with a case which was observed in the same year by Thorne⁴ and Robinson, was later described in detail by Rixford and Gilchrist⁵. Posadas and Wernike, as well as Rixford and Gilchrist, believed that the infecting organism was a protozoan belonging to the group of *Coccidia*, and on that account the latter authors suggested the name of *Coccidioides immitis*. In 1900 another case was observed by Ophuls and Moffitt,⁶ who found that the parasite grew readily on artificial mediums, and that it developed as a mold which apparently belonged to the group of *Oidia*. Ophuls⁷ then suggested the names *Oidium coccidioides* for the parasitic organism and coccidioidal granuloma for the lesions which it produces.

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1 Posadas Psorospermiose Infectante Generalisee, Rev de Chir, 1900, xxi, 277

2 Wernike Ueber einen Protozoandefund bei Mycosis fungoides, Centralbl f Bakteriöl, 1892, xii, 859

3 Rixford Case Demonstration, Occid Med Times, 1894, viii, 326

4 Thorne, W S A Case of Protozoic Skin Disease, Occid Med Times, 1894, viii, 703

5 Rixford and Gilchrist Two Cases of Protozoan (Coccidioidal) Infection of the Skin and Other Organs, Johns Hopkins Hosp Rep, 1, 211

6 Ophuls and Moffitt A New Pathogenic Mould, Philadelphia Med Jour, 1900, v, 1471

7 Ophuls Further Observations on a Pathogenic Mold Formerly Described as a Protozoan, Jour Exper Med, 1905, vi, 443

In July, 1914, MacNeal and Taylor⁸ collected the reports of twenty-four cases which had been recorded in the literature before March of the same year, but they overlooked one case which had been reported by Evans⁹ in 1909 and another which had been reported by Chipman¹⁰ in 1913. Since the publication of their report, Roblee¹¹ has reported one case, Cooke¹² has reported two, and Brown and Cummins¹³ have reported two, so that in all there have been thirty-one established cases recorded in the literature. In the Pathological and Bacteriological Laboratories of Leland Stanford Junior University, School of Medicine (formerly Cooper Medical College), sixteen cases of coccidioidal granuloma have been studied. Six of these have been reported by Ophuls,¹⁴ one by Bowles¹⁵ and one by Chipman,¹⁰ but there still remain eight hitherto unrecorded cases, four of which were studied by Ophuls and four by Ophuls and myself, which form the basis of the present report. In addition to these, there is one more case which was observed by S. J. Gardner and H. W. Gibbons, to whom I am indebted for the clinical and pathologic records.

The origin of the infecting organism is unknown, but it is of considerable interest that of the forty known patients, thirty-five had been residents of California, and three had visited the state. Twenty-seven of the patients had been residents of or had spent some time in the San Joaquin Valley, and of the eight other persons who developed the disease in California, there are but two of whom there is record that they had not been in the San Joaquin Valley.

The majority of cases have occurred in laboring men. Thirty-seven were in adult males, one in a male child about 3 years of age, and two were in women. There is no apparent racial susceptibility, since persons of various nationalities have been affected.

The mode of onset varies in different cases, the most striking feature being the remarkably close resemblance to tuberculosis which

8 MacNeal and Taylor. *Coccidioides Immitis* and Coccidioidal Granuloma, *Jour Med Research*, 1914, xxx, 261.

9 Evans. Coccidioidal Granuloma and Blastomycosis in the Central Nervous System, *Jour Infect Dis*, 1909, vi, 523.

10 Chipman, E. D. The Newer Cutaneous Mycoses, *Jour Amer Med Assn*, 1913, lxi, 407.

11 Roblee. Report of a Case of Oidiomycosis, *California State Jour Med*, 1914, xii, 390.

12 Cooke, J. V. Immunity Tests in Coccidioidal Granuloma, *THE ARCHIVES INT MED*, 1915, xv, 479.

13 Brown, P. K., and Cummins, W. T. A Differential Study of Coccidioidal Granuloma and Blastomycosis, *THE ARCHIVES INT MED*, 1915, xv, 608.

14 Ophuls, William. Coccidioidal Granuloma, *Jour Am Med Assn*, 1905, xlv, 1291.

15 Bowles, F. H. Coccidioidal Granuloma, *Jour Am Med Assn*, 1912, lix, 2253.

is evident in the initial lesions as well as in the clinical course and in the pathologic picture. In a considerable number of the reported cases, the initial lesions occurred in the skin as nodular, granulomatous areas in the corium which usually ulcerated and gradually increased in size. In the majority of the remaining cases, the initial symptoms indicated primary pulmonary infection, and strongly suggested pulmonary tuberculosis, but in a few cases the first lesions occurred in the joints, and in at least three of our series of cases a diagnosis of tuberculosis of the joints had been made. It is a point of considerable interest that in two of our cases the joint lesions developed immediately after trauma.

The primary skin lesions usually appear as small, indurated nodules which may be quite painless, but which gradually enlarge and finally show small collections of pus on the surface. After ulceration occurs, a dirty crust forms, and the lesion slowly increases in size by extension at the edges. Beneath the crust is a ragged, nodular, granulomatous surface which shows numerous small accumulations of pus, and from which often a large amount of pus can be squeezed. Usually there is fairly early involvement of the regional lymph nodes which may or may not be painful. The appearance of the skin lesions so closely resembles the more acute forms of cutaneous tuberculosis in the gross and in microscopic sections that diagnosis can be made only by the identification of the characteristic spherical bodies in the pus or in the tissues, or in the cultivation of the fungus. The lesions may remain localized in the skin for a considerable length of time, in Posada's case seven years and in Rixford's first case nine years, but, with one exception, in all of the reported cases in which they first appeared in the skin, a general infection eventually occurred.

When the initial infection occurs in the respiratory tract, the clinical picture is that of pulmonary tuberculosis. The patients usually complain of cough, weakness, loss of weight, gastro-intestinal disturbances, fever and night sweats. There is frequently blood-stained sputum in which, however, no tubercle bacilli can be found. There is recorded but one exception to the latter characteristic. In the case reported by Chipman,¹⁰ the diagnosis of coccidioidal granuloma was established by microscopic examination of tissue from a lesion of the skin, but tubercle bacilli were found in the sputum on at least two occasions by different observers. It is unfortunate that necropsy was not permitted in this case. Physical examination shows all the signs of pulmonary involvement, and pleural effusion is often found. Unless one thinks to examine the fresh sputum for the spherical bodies of coccidioidal granuloma, a diagnosis of pulmonary tuberculosis will almost surely

be made. In cases in which pulmonary lesions have occurred, the onset of the general infection rapidly ensues.

One case is reported by Carson and Cummins,¹⁶ in which a diagnosis of tuberculous laryngitis was made a few months before the onset of the terminal general infection, but in this case complete necropsy was not permitted, and it was impossible to determine the nature of the lesion in the larynx.

When the infection first manifests itself in the joints, the picture is that of an acute or subacute arthritis, and, as stated before, it is interesting that in some of the cases the arthritis developed immediately after trauma to the parts affected. The joints are swollen, red and painful, and eventually become fluctuating. Roentgen-ray examination reveals a type of bone destruction which is indistinguishable from tuberculosis. If incision is made into the fluctuating mass, or if spontaneous rupture occurs, a large amount of creamy and sometimes blood-stained pus escapes, and even though the walls of the abscess and the bone be thoroughly curetted, the sinuses usually refuse to heal. In the joint cases, as in the skin cases, the regional lymph nodes soon become involved, but in the former there is the greatest hope of successful treatment, since the progress of the disease has been arrested in two cases which were treated by Gardner by early amputation of the foot and resection of the elbow joint, respectively.

The almost constant outcome of the disease is general infection with rapidly fatal termination. There are, in so far as is known to the author, only four cases in which a clinical diagnosis had been established which did not progress to a general infection. One of these patients (Case 39) is still living about two years after the appearance of the initial symptoms, but it is as yet too soon to say what the outcome will be, especially as there is still evidence of an active process in one knee. Another patient (Case 33), who was apparently cured, died of an intercurrent disease about two years after he seemed to be well, but as no necropsy was performed, it is impossible to say that complete recovery had taken place. The other two cases are those in which Gardner¹⁷ performed early operation, and in these there was apparently a complete arrest of the process.

The symptoms of the patients with a general infection vary according to the distribution of the lesions in the body. In those cases in which there are no skin lesions, the clinical picture resembles that of miliary tuberculosis or of typhoid fever. When skin lesions are

¹⁶ Carson, G. R., and Cummins, W. T. A Case of Coccidioidal Granuloma, *Jour. Am. Med. Assn.*, 1913, lxi, 191.

¹⁷ Gardner, S. J. An Unusual Infection in the Bones of the Foot, *California State Jour. Med.*, 1904, ii, 386.

present, the condition often resembles malignant syphilis or glanders. In one case,¹⁸ that which occurred in a child, the terminal symptoms were those of meningitis, and the patient was treated for cerebrospinal meningitis. It can be said, however, that usually there is extreme exhaustion, high fever, often of a septic type and accompanied by chills, frequent severe night sweats, progressive emaciation and anemia and a moderate leukocytosis. Quite frequently there is the formation of large, painless abscesses in the subcutaneous tissues which develop suddenly and usually burst and liberate large amounts of creamy pus. The sinuses which are so formed rarely close. Death usually occurs from exhaustion.

In the pathologic picture even more than in the clinical manifestations does this disease resemble tuberculosis. In several of the cases, the anatomic diagnosis at necropsy has been tuberculosis, and it was only when microscopic examination was made that the true nature of the condition was recognized. The individual lesions consist of typical tubercles with central caseation, multinuclear giant cells of the Langhans type, epithelioid cells and lymphocytes. In the lungs and in the abdominal organs and lymph glands there is usually marked caseation and comparatively little abscess formation, although in some of the tubercles one sometimes sees the small, central accumulations of leukocytes which are often seen in acute tuberculosis. When the bones and subcutaneous tissues are involved, there is much pus formation, and the contents of the abscesses are more truly pus than is the case in tuberculous abscesses, in that a fairly large number of true pus-cells are present. In the cases in which general infection has occurred, the usual picture is that of an acute, disseminated, miliary tuberculosis, and numerous tubercles are found in all parts of the body. It is not at all unusual to find a basilar meningitis which is indistinguishable from tuberculous meningitis, in which the distribution of the tubercles is confined to the basal meninges and to the folds of the meninges within the basal portions of the sulci. Evans⁹ has pointed out that in this respect there is a distinct difference from blastomycotic involvement of the central nervous system, in which the lesions are found in the substance of the brain and of the cord.

A peculiar feature is the tendency to involve testicular tissue. This has been noted in a number of the human cases, but is much more noticeable in animals. If infection is produced in male animals by intraperitoneal injection, there is early involvement of the testicles which become swollen and hard and which soon suppurate and dis-

¹⁸ Ryfkogel, H. A. L. Coccidioidal Meningitis. Jour. Am. Med. Assn., 1910, 1v, 1730.

charge through sinuses. This phenomenon is as characteristic as in glanders, and affords early evidence of successful inoculation.

The parasitic organisms which cause the disease are easily found in the tissues, in the pus and in the sputum. They appear as spherical bodies about 30 microns in diameter with double-contoured capsules and a slightly granular protoplasm which is sometimes vacuolated. The capsule is highly refractile, and in some cases seems to have short knobs or prickles on the outer surface. A true nucleus has never been demonstrated. In the tissues these spherical bodies are found in the diseased areas in large numbers, usually within the tubercles, and frequently inside the multinuclear giant cells. In the walls of the abscess cavities and in the pus they are usually very numerous, and can be demonstrated with little difficulty. In the pus or in the sputum they are best seen in a fresh specimen prepared by placing a coverslip over a drop of the material on a glass slide. If examination is made with but little light, the spherules stand out prominently and are easily distinguished from cells and from the myelin droplets which are also usually present. The bodies stain poorly with the ordinary staining methods, and are very apt to be overlooked in the stained smear.

Reproduction within the tissues occurs by a process of endosporulation, and the organism differs from the blastomyces in that true budding has never been observed. The spores develop by a division of the protoplasm within the capsule until a large number, a hundred or more, are formed, and when mature they are so closely packed together that they assume various shapes. They are released through a rupture in the capsule of the parent body, and it is not at all uncommon to find a number of the empty envelopes in a specimen of pus. The development of the adult forms from the spores has not been definitely traced because the spores are so small and they stain so poorly that it is impossible to follow the changes that occur after they escape from the parent body. However, Ophuls⁷ was able to find a few cases in which the spores seemed to mature within the body of the parent before rupture of the capsule liberated them, and he believes that the adult forms develop directly from the spores by simple growth without further change than the formation of the relatively thick, double-contoured capsule.

On artificial culture mediums the organism develops as a white mold with short aerial hyphae in which chlamydospores develop. The transition from the spherical body that occurs in the tissues to the hyphae of the growth on the artificial culture mediums was first demonstrated by Ophuls¹⁹ by studying cultures prepared by mixing the

19 Ophuls and Moffitt. A New Pathogenic Mold, *Philadelphia Med Jour* 1900, v, 1471. Ophuls. Further Observations on a Pathogenic Mold Formerly Described as a Protozoan, *Jour Exper Med*, 1905, vi, 443.

pus with the culture mediums in a hang-drop preparation. He found that if the spherical body was surrounded by even the smallest particle of tissue, no hyphae formation occurred, but that if it was free in the mediums, the hyphae developed by a process of outgrowth through the capsule. Sometimes but one hypha developed from a single sphere, but at other times there were several hyphae arising from different parts of the capsule. He was not able to find any evidence of endosporulation in the cultures.

Various attempts have been made to trace the development of the spherical bodies from the fungus form. Ophuls⁷ found that if a fresh culture in which spore formation had not yet taken place was injected into susceptible animals no infection followed, but that if a spore-bearing culture was injected, practically all of the animals became infected. He concluded that the spherical bodies in the tissues must be derived in some way from the spores of the fungus, since in all cases there was rapid destruction of the hyphae that were injected. Wolbach²⁰ concluded from his experiments that the spherical bodies were developed directly from the mycelium, and that each sphere was derived from a single segment. MacNeal and Taylor⁸ arrived at the same conclusion by a slightly different method of procedure, but it does not seem probable that the question is yet settled. Neither Wolbach nor MacNeal and Taylor mention having taken any precaution to make sure that they were injecting pure mycelia in which no spores were present. The presence of spores in some of the mycelial segments may readily explain why these particular segments survived when the great majority of those which were injected underwent rapid disintegration.

The only record of immunity tests in coccidioidal granuloma is that published by Cooke,¹² who made an exhaustive study of a case which was recently under observation at the University of California Hospital. In the summary of his report he says

In a case of coccidioidal granuloma studied, no specific complement-fixing bodies or agglutinins could be found in the blood serum. No specific skin reaction could be demonstrated. Precipitins, however, could be demonstrated in the serum even when diluted 1:160, when an extract of dried cultures of the organism was used as precipitinogen. These precipitins were apparently specific.

There has been considerable difference of opinion as to the relationship which exists between coccidioidal granuloma and blastomycosis. European authors and a number of American authors from the Eastern and Middle Western States are inclined to believe that the

²⁰ Wolbach. The Life Cycle of the Organism of Dermatitis Coccidioides, Jour. Med. Research, 1904, xiii, 53.

two conditions are practically identical. At least two of the cases of coccidioidal granuloma have been reported as blastomycosis,²¹ although in one it was noted that it was an unusual type of blastomycosis in that reproduction occurred in the tissues by a process of endosporulation. Hyde²² has suggested that the difference in the method of reproduction in the two conditions may be due to the fact that climatic conditions are different in the localities in which each is found. It is probable that he based his conclusion on the fact that in a case of blastomycosis in which the infection had become general, the patient completely recovered after removal to the southern part of California, for in relating the history of the case he says

If this result be due simply to climatic influence, it would seem to bear out the conclusions of those who have studied the phenomena of the disease, viz that the organisms are chiefly effective when developing in an environment favorable to their fructification.

That climate does not play so important a part in determining the character of the organism is shown by the fact that there have been a number of cases of true blastomycosis in California. In 1906, MacGowan²³ reported a case which he had observed in Southern California. In 1913, the author in collaboration with Dr. Harold P. Hill,²⁴ reported a case which had developed in the northern part of the state, and in the present report is the record of a case which developed in Michigan but which, after temporary improvement, progressed to a fatal termination in the San Joaquin Valley. In addition to these is an interesting series of cases which Dr. T. M. Williams of Palo Alto discussed before the California State Society meeting in 1914. In Williams' series of three or four cases the lesions were confined to the region of the finger nails and developed as onychiae. The infection remained localized in every case, but was so severe as to cause the loss of the nails in several instances. In at least one of the cases there have been mild recurrences every few months, but the lesions have always subsided on the application of tincture of iodine. Bacteriologic examination of the pus in these cases was made by Dr. Hans Zinsser, and all showed a typical blastomyces which grew in the usual way on culture mediums. With the exception of Williams' cases, those which occurred in Califor-

21 Morris, R. T. A Case of Systemic Blastomycosis, *Jour. Am. Med. Assn.*, 1913, lxi, 2043. Powers, Systemic Blastomycosis, *Tr. Am. Surg. Assn.*, 1914, p. 89.

22 Hyde, Correspondence Respecting Blastomycosis, *Jour. Cutan. Dis.*, 1907, xxv, 34.

23 MacGowan, Case Report of Blastomycosis, *South California Pract.*, 1906, xxi, 148.

24 Hill, H. P., and Dickson, E. C. Report of a Case of Systemic Blastomycosis, *California State Jour. Med.*, 1914, xii, 120.

nia differed in no respect from the cases which have been described elsewhere, and they prove conclusively that Hyde's explanation for the differences in the method of reproduction in *Oidium Coccidioides* and blastomycosis is not correct

Hektoen,²⁵ MacNeal and Taylor⁸ and Brown and Cummins¹³ have made experimental comparative studies of the two conditions, and they all agree with those who are familiar with the clinical cases of coccidioidal granuloma in believing that the two are distinct diseases, although they are closely related. The mere fact that both grow as similar fungi on artificial culture mediums is not sufficient ground for considering them identical. The constancy with which the characteristic methods of reproduction in the tissues is adhered to in each, irrespective of climatic influences, as well as the recognized differences in the clinical course of each would seem to be sufficient evidence that the two conditions are distinct. That they are closely related, however, there can be no doubt, and it seems quite probable that Ricketts²⁶ was correct when he said that "the differences between these diseases may all be explainable on the score of specific variations of the fungi concerned."

Diagnosis can be made only by the demonstration of the characteristic endosporulating bodies in the tissues, pus or sputum. The clinical picture is so varied, and the resemblance to tuberculosis and blastomycosis is so great, that one cannot depend on the clinical manifestations alone in making a diagnosis. The demonstration of the parasites is usually so easy that one has but to think of the disease and to make the necessary laboratory examinations to establish its identity. I believe that if a routine examination for the *Oidium coccidioides* were made in all cases of clinical tuberculosis in which the tubercle bacilli cannot be found, the number of recognized cases of coccidioidal granuloma would soon be greatly increased.

The prognosis is extremely grave. The outcome of the disease is almost always fatal. The duration varies from a few months to several years after the onset of the initial symptoms, but as a rule death follows in a few weeks or months after the infection becomes general. That recovery can take place is shown, however, by the two cases in which early operation was performed, and by an exceedingly interesting case (Case 38) which is included in the present series. The patient was a German laborer, aged 59, who entered the hospital complaining of severe gastro-intestinal disturbances. A diagnosis of car-

25 Hektoen Ludwig. Systemic Blastomycosis and Coccidioidal Granuloma, Jour Am Med Assn, 1907, xlix, 1071

26 Ricketts. Oidiomycosis (Blastomycosis) of the Skin and Its Fungi, Jour Med Research, 1901, vi, 373

cinoma of the stomach was established and gastro-enterostomy was done. He developed a postoperative pneumonia and died a few days later. At necropsy an old caseous focus which was surrounded by dense fibrous tissue was found in the base of the right lung. A diagnosis of "healed" tuberculosis of the lung was made, but on microscopic examination it was found that a number of typical spherical bodies of *Oidium coccidioides* were present, and that no tubercle bacilli could be demonstrated. There was no other evidence of any lesion which resembled tuberculosis.

Treatment is most unsatisfactory. The only hope seems to be in early amputation when the initial lesion is situated on one of the extremities and when there has been no further progression. In one of Gardner's cases, resection of the joint was sufficient to arrest the further progress of the disease, but it is probable that had the diagnosis been made before operation, more radical procedures would have been adopted. Roentgen-ray treatments have been tried in a few cases (Montgomery and Morrow²⁷ and Case 40), but, although there seemed to be some improvement in the local lesions, the onset of general infection was not prevented. Iodin, which is of value in blastomycosis, is of little aid in coccidioidal granuloma.²⁸ Autogenous vaccines have been tried, but they produced no beneficial effect. Neo-salvarsan was tried by Cooke¹² without any signs of improvement. In fact, nothing that has been attempted in medication has had any appreciable effect in allaying the progress of the disease.²⁹

CASE REPORTS

1 COCCIDIOIDAL GRANULOMA

CASE 32—Mr. D., a patient of Dr. Rixford's, was treated in Lane Hospital, San Francisco, during the spring and summer of 1907. The clinical record is unknown to me, but the following data are recorded in reports of the Pathological Laboratory. All the examinations were made by Dr. Ophuls.

April 20, 1907, a specimen from a resected knee was examined. Sections showed a marked formation of granulation tissue and extensive destruction of the cartilage. There were many tubercles in the synovial membrane, and many adult forms of the spherical bodies of *Oidium coccidioides*. Cultures showed the typical mold growth.

²⁷ Montgomery, D. W., and Morrow. Reasons for Considering Dermatitis Coccidioides an Independent Disease, Jour Cutan Dis., 1904, xxii, 368.

²⁸ Cooke (Footnote 12). Brown and Cummins (Footnote 13). Hektoen (Footnote 25). Brown, P. K. Coccidioidal Granuloma, Jour Am Med Assn., 1907, xlviii, 743.

²⁹ In addition to the references already given, the following will be found of interest: Montgomery, D. W., Ryfkogel and Morrow. Dermatitis Coccidioides, Jour Cutan Dis., 1903, xxi, 5. Montgomery, F. H., and Ormsby, O. S. Systemic Blastomycosis. Its Etiologic, Pathologic and Clinical Features as Established by a Critical Survey and Summary of Twenty-Two Cases, Seven Previously Unpublished, the Relation of Blastomycosis to Coccidioidal Granuloma, THE ARCHIVES INT. MED., 1908, 11, 1.

In May of the same year, scrapings of tissue from the wrist and from the knee showed much granulation tissue and much cicatricial tissue with many tubercles and large caseous areas. In the giant cells of the tubercles were many parasites in various stages of development. Pus from the wrist showed many endosporulating forms.

July 3, sections of recent lesions of the skin and scrapings from the wrist, knee and leg were examined. Sections from the skin showed marked cellular infiltration and formation of granulation tissue in the papillary layer of the cutis. There was marked irregular growth of the epithelium, which extended far into the granulation tissue, and there were several small abscesses containing parasites. The granulation tissue from the wrist showed many tubercles with extensive caseation and many giant cells.

CASE 33—J. C., a French farm laborer, had lived near Colusa, Calif., for nearly twenty years. In the autumn of 1907 he went to the southern part of the state, "near Los Angeles," to assist in walnut picking. In January, 1908, he consulted Dr. C. A. Poage of Colusa on account of an abscess between the thumb and index finger of the hand. At the same time a small abscess developed on the side of the face, near the ear. Both lesions were opened and drained, but they refused to heal although numerous incisions were made. A few months later a similar lesion appeared on the dorsum of one foot. This was also incised, but did not heal. In May, 1908, the patient was referred to Dr. Stanley Stillman of San Francisco, who curetted the abscesses and sent the tissues to Dr. Ophuls for examination.

Sections showed vascular granulation tissue in which were many submiliary nodules consisting of epithelioid cells, with central caseation. Many mature forms of the *Oidium coccidioides* were found.

The patient complained of persistent cough and profuse expectoration, and on two occasions the spherical bodies of *Oidium coccidioides* were found in the sputum. Repeated examinations for tubercle bacilli proved negative.

The abscesses remained open and discharging, and the cough persisted until December, 1908, when the general health of the patient improved, the wounds healed and the cough disappeared. During the following year and until February, 1910, he remained in fairly good health and was considered cured, but at that time he began to show symptoms of subacute nephritis, and he died in November of the same year. During the terminal illness there was no evidence of recurrence of the skin lesions or of the pulmonary condition. Necropsy was not permitted.

CASE 34—C. F. J., an Australian sailor aged 39, was admitted to the San Francisco Hospital, Feb. 14, 1909, on the service of Dr. J. B. Frankenhimer. The family history and the previous personal history were negative so far as the terminal illness was concerned. In October, 1909, the patient had obtained work as a rope-splicer in the oil fields of Kern County in the San Joaquin Valley. In December of the same year he began to cough, and in January, 1910, he became "short of breath" on exertion. Previously to that time he had had no fever, hemoptysis or night sweats.

On admission to the hospital he complained of pain in the left side of the chest, cough with free expectoration, frequent night sweats and a loss of 22 pounds in weight during the past three weeks. He had noticed some slight abrasions of the skin which had been obtained while he was working and which had become infected, but they had not been sufficiently severe to attract especial attention, and they had all cleared up before he came to the hospital.

The patient was moderately anemic, somewhat cyanotic and slightly dyspneic. There was a pleural effusion in the left side of the chest which reached the level of the fifth dorsal vertebra posteriorly, and which had displaced the heart so that the right margin of the area of cardiac dulness was well to the right of the right sternal margin. There was no evidence of cardiac valvular involvement, and the cardiac muscle tonus was not impaired. The liver and

the spleen were palpable. The skin was clear, the superficial lymph nodes were not enlarged, and the reflexes were normal.

Two thousand cubic centimeters of fluid were withdrawn from the pleural cavity, but it rapidly reaccumulated and was removed again within two weeks. The fluid on both occasions was clear and contained no demonstrable bacteria. Cultures were negative.

The Moro skin reaction was positive, but repeated examinations of the sputum revealed no tubercle bacilli. The urine was in no way abnormal. The red blood corpuscles numbered 4,800,000, and the leukocytes numbered 12,000. The differential count showed 87 per cent polymorphonuclear neutrophils, 7 per cent lymphocytes, 4 per cent large mononuclear cells, 2 per cent eosinophils and 1 per cent basophils.

Early in June an enlarged gland was noticed under the sternocleidomastoid muscle, immediately above the sternoclavicular joint on the right side, and it rapidly increased in size and became very tender. At this time the patient was very weak, his appetite was poor and he had a very severe cough and many night sweats. Dulness was noted at the root of the right lung, and there were numerous moist râles in the right upper lobe. June 7, the gland was excised, and an abscess from which about 2 ounces of creamy pus escaped was revealed at the apex of the right pleural cavity. Sections of the gland were examined by Dr. Ophuls, who made the diagnosis of coccidioidal granuloma of the cervical lymph glands. The characteristic endosporulating forms were found in the tissue, and cultures showed a pure growth of the fungus. Subsequent examinations of the sputum showed numerous endosporulating forms of the *Oidium coccidioides*.

The patient gradually became weaker and there was progressing evidence of pulmonary involvement. A large tumor appeared under the left sternocleidomastoid muscle, and the cervical and inguinal lymph nodes became enlarged. The fever was intermittent and remittent in character, and was usually about 101 F in the afternoon but occasionally reached 103. The respirations varied between 20 and 26, and the pulse between 90 and 116. The patient died, July 31, 1910.

Necropsy was performed by the author about twenty-four hours after death. Examination showed a general infection with the *Oidium coccidioides* involving the meninges, lungs, pleura, cervical, mediastinal and retroperitoneal lymph nodes, liver, spleen, kidneys, ribs and sternum. The macroscopic appearance of the lesions in the soft tissues was identical with that of tuberculosis, but in addition there were large abscess cavities in the neck and between the parietal layer of the pleura and the ribs which were filled with thick, creamy pus. Microscopic examination of the tissues revealed numerous spherical bodies with double-contoured capsules, many of which contained spore-like bodies. Cultures from the pus showed pure growths of the characteristic fungus. No tubercle bacilli were found in spite of prolonged search. The lesions were reproduced in guinea-pigs by inoculation of pus into the peritoneal cavity, and the fungus was again grown in pure culture from them.

CASE 35—J. E. F., a brakeman on the Southern Pacific Railway lines in the San Joaquin Valley, was admitted to the Southern Pacific Hospital in San Francisco, July 8, 1911, complaining of a stiff and painful elbow. He stated that in 1902 he had received a blow on the elbow and that since that time he had constantly suffered pain. This had become progressively worse until one month before admission to the hospital, when it was so severe that he was forced to stop work.

On examination it was found that the right elbow was completely ankylosed and that there was marked atrophy of the muscles of the arm. There was no other evidence of disease. Local applications of heat and of high-frequency electricity were tried without benefit. August 8, resection of the elbow was performed by Dr. S. J. Gardner. Microscopic examination of the tissue was

made by Dr H W Gibbons and Dr Ophuls, who found that there was much granulation tissue with typical tubercle-like nodules, in some of which were the characteristic spherical bodies of *Oidium coccidioides*

The patient made a slow recovery, but finally returned to work and has regained a fairly good use of the arm. He was still in good health a few months ago, and has shown no evidence of recurrence

CASE 36—N S, a Hindu laborer aged 26, admitted to the surgical ward of Lane Hospital, May 25, 1912. But little was learned of his previous history excepting that he had recently been in a hospital in Stockton on account of a condition of the knee which was thought to be tuberculosis. On admission to Lane Hospital, the patient was much emaciated and there was an open wound in the left knee from which much foul-smelling pus escaped. May 29, the knee was resected, but the wound continued to discharge much pus and the patient failed to improve. He complained of great pain in the knee and subsequently of pain in the left elbow, which became swollen and stiff. He remained in the hospital until August 27, when he died.

Necropsy was performed by Dr Ophuls about twenty-four hours after death. Examination revealed a general infection with the *Oidium coccidioides*, involving the lungs, pleura, cervical, mediastinal and peribronchial lymph nodes, synovial membranes of the left elbow and the lumbar vertebrae. There was marked caseous destruction of the bodies of the vertebrae, and an abscess cavity extended along the course of the left iliopsoas muscle into the pelvis. Smears of the pus and of scrapings from the peribronchial lymph nodes and from the synovial membrane showed many characteristic endosporulating forms of the *Oidium coccidioides*. No tubercle bacilli were found. Sections of the tissues showed the typical tubercle-like nodules and many of the spherical bodies.

CASE 37—A Mexican laborer who could speak no English was seen by Dr T M McNamara of Bakersfield in the autumn of 1912. The patient was practically moribund when first seen, and no history could be obtained. Necropsy was performed by Dr McNamara, who found a condition which resembled disseminated miliary tuberculosis. Portions of the lung and of the spleen were sent to the author for microscopic examination. Sections showed numerous lesions which resembled tubercles, but which contained many double-contoured bodies of the *Oidium coccidioides*. No tubercle bacilli were found.

CASE 38—J U, a German laborer aged 59, was admitted to the medical ward of Lane Hospital, July 19, 1913. He complained of "pain in the bowels," which came on about four hours after eating and which was relieved by pressure. He had lived in Germany, the Sandwich Islands and California, but there is no record of what parts of California he had visited. Diagnosis of duodenal obstruction was made, and laparotomy was performed, August 5. At operation an inoperable carcinoma of the stomach was found, and gastro-jejunostomy was done. August 15, the patient contracted pneumonia, and he died a few days later.

Necropsy was performed by Dr E D Downing about twenty-four hours after death. Examination revealed a large polypoid carcinoma situated on the lesser curvature of the stomach near the pylorus. There was a well-marked pneumonia of the left lower lobe, and an area of gangrene in the right upper lobe. In the base of the right lung was an old caseous focus which was surrounded by dense fibrous tissue and which was thought to be a "healed" tuberculous process. However, microscopic examination made by Dr Ophuls was recorded as follows: "A section of the lung shows large, old, caseous areas surrounded by dense fibrous tissue. At the edge of the caseous material there are a number of double-contoured capsules of the *Oidium coccidioides*. The majority of them are empty, but some contain a little granular protoplasm. Diagnosis: healed coccidioidal granuloma of the lung." No other foci of coccidioidal granuloma were found.

CASE 39—In August, 1913, Mrs H, an American housewife aged 65, consulted Dr John E Veon of Bakersfield, Calif, complaining of pain in the left ankle which had persisted for eight weeks. A localized tender swelling was found immediately above the outer malleolus, and there was daily intermittent fever which ran from 100 to 103 F. In November, 1913, the tumor was incised and a small abscess was drained. The wound refused to close. In February, 1914, the bone was curetted, and the material was sent to Dr Ophuls for examination. Sections showed the characteristic lesions of coccidioidal granuloma, in which were many of the usual spherical endosporeulating bodies.

About this time the patient complained of pain in the right knee, but this soon disappeared and remained absent for about six months. The abscess cavity in the left ankle gradually healed after prolonged treatment with liquor formaldehydi, tincture of iodine and Beck's paste. During the summer of 1914 the patient was free from symptoms, but about September 1 she began to complain of a recurrence of pain in the right knee. At the last report, a few months ago, the knee was swollen, hot and painful, and there were four small painful nodules on the shaft of the right tibia, but the patient appeared to be normal in all other respects.

CASE 40—J D, a Jamaican negro sailor aged 21, came to the Outpatient Department of the Leland Stanford Junior University, School of Medicine, Jan 31, 1914, complaining of a sore foot. He appeared to be in great pain and was unable to put the right foot to the ground. There was an area of discoloration on the dorsum of the foot in the region of the middle cuneiform bone. The whole foot was swollen and somewhat tender, the greatest tenderness being located immediately beneath the discolored area. A diagnosis of arthritis of doubtful origin was made, and the patient was sent to the San Francisco Hospital where he was admitted to the Surgical Service of the Leland Stanford Junior University, School of Medicine. At the time of admission, a tentative diagnosis of tuberculosis was made.

The patient dated his illness from a time two years previously when he had been suspended by the feet for several hours in Honduras. He came to California in July, 1913, and soon after his arrival he went to Coalinga where he worked in the oil fields for four months. During that time he had no cough and he felt practically well. In November, 1913, he returned to San Francisco, and, a few days later, following exposure from sleeping outdoors, he began to cough. There was no fever and no blood in the sputum at that time.

November 11, a heavy iron girder fell on his right foot, and he was forced to stop work. The foot became swollen, and pained considerably. He treated at home for about two weeks by applying liniments, but although the pain disappeared, the swelling persisted. He then consulted a physician, who had a Roentgen-ray examination made and who placed the foot in a plaster cast. The pain continued to be so severe that the patient insisted on removing the cast, and he was therefore discharged from the hospital in which he was being treated.

A few days after his admission to the San Francisco Hospital, the skin over the tender area broke and there was a profuse discharge of bloody pus. The foot was again placed in a plaster cast, but the discharge did not cease. March 3, the patient was removed to Lane Hospital, where Roentgen-ray examination was made and a diagnosis of tuberculosis of the tarsal bones was given. Several Roentgen treatments were given at this time, and another series was given during the interval between April 3 and 20, but although the treatments relieved the pain to a certain extent, the suppuration continued and new sinuses formed. During the time that he was in Lane Hospital, the temperature was septic in type, varying from 98 to 99 F in the mornings and from 102 to 103 in the afternoons. The same type of temperature persisted after he returned to the San Francisco Hospital, and he steadily lost weight and strength.

May 2, Dr Rixford amputated the foot and curetted the pockets, which had extended along the course of the tendons. The general condition improved

after the operation, and the patient began to gain in weight. During June and July, fluctuating masses appeared on the right side of the chest, on the side of the left leg and in the right arm. These were still present when the patient left the hospital in September, although he felt and looked quite well. After leaving the hospital, the patient left San Francisco for New York, and it is supposed that he is now in Jamaica.

Bacteriologic examinations of the pus were made by me with the assistance of Dr. E. G. Cary. March 19, 1914, a specimen of pus from the foot was examined. The smear showed a moderate number of pus cells and of lymphocytes and a few large mononuclear cells. There was a moderate amount of fibrin. No tubercle bacilli or other bacteria were found, and no spherical bodies of the coccidioidal type were seen. The culture on agar agar was reported negative after forty-eight hours, but some time later a growth of mold was found in the tube. A portion of the pus was injected into the peritoneal cavity of a guinea-pig, but no lesions were found when the animal was killed a month later.

June 3, another specimen of pus was obtained, and in this a few atypical spherical bodies with double-contoured capsules were found. No bodies containing endospores were seen. Culture of this specimen showed the characteristic mold growth in a few days, and in a hang-drop culture the development of the mycelial threads from the spherical bodies was observed. Two guinea-pigs and one rabbit were inoculated with the pus and in all, after one month, the characteristic lesions of coccidioidal granuloma were found. Pus from the lesions in all the animals contained the typical endosporulating bodies, and cultures showed pure growths of the fungus. No tubercle bacilli or other bacteria were found in the original pus or in that obtained from the lesions in the animals.

2 SYSTEMIC BLASTOMYCOSIS

CASE 1 (Previously reported by Hill and Dickson²⁴)—A. S., a Greek laborer aged 28, was admitted to the San Francisco Hospital on the Stanford University Medical Service, July 6, 1912. He had been working at McCloud, Calif., during the summer months and in the Sacramento Valley during the winters. Six months before admission, while working at McCloud, he "caught cold and began to spit blood." The "cold" lasted for two months. One month later he noticed a swelling under the left lower eyelid, and this was followed by similar swellings on the forehead, face, arms and legs. At intervals the swellings on the face would open, discharge a quantity of pus and dry up. The patient gradually lost weight and strength, although there was no loss of appetite.

At the time of admission, the patient was emaciated, pigmented and covered with nodular masses, discharging ulcers and dried crusts. There was a slight cough and much mucopurulent sputum, which was occasionally streaked with blood. The cervical lymph nodes were shotty. Fluctuating masses were situated under the skin in various parts of the body, and there were numerous discharging ulcers and scars of old ulcers. The skin over the fluctuating masses was normal in color excepting at the point of rupture, and these areas were rarely painful or tender, excepting around the joints. The abscesses showed a marked tendency to involve the deeper tissues and the bone. There was evidence of extensive involvement of both lungs.

Examination of the aspirated pus was made by Dr. Ophuls, who found typical budding forms of blastomyces, and subsequently similar forms were found in large numbers in the sputum. Repeated examinations for the tubercle bacillus were negative.

The course was that of a chronic pyemia with septic temperature, progressive emaciation and loss of strength. There were numerous recurring abscesses involving the subcutaneous tissues, deeper tissues, bones and testicles. Death occurred about six months after admission to the hospital.

Necropsy was performed by the author about twenty-four hours after death. Examination showed a general infection with blastomyces involving the skin, subcutaneous tissues, bones, cartilages, lungs, kidneys and testicles. A peculiar type of bone involvement was noted in the ribs, where superficial subcutaneous abscesses were found to be continuous with intrathoracic abscesses through perforations in the ribs, while the soft intercostal tissues remained intact.

Smears from the pus from the various abscesses showed numerous budding forms of the blastomyces, and cultures showed fungus growth. Sections of the tissues showed many small tubercle-like nodules in which were the characteristic spherical and budding forms. No tubercle bacilli were found in the pus or in the lesions in the tissues.

Several guinea-pigs and rabbits were injected with the pus, but in none were any lesions found. Inoculation of animals with the fungus also proved negative.

CASE 2—D McC consulted Dr J L Mudd of Merced, Calif, in the summer of 1911 because of a pustular eruption on the thumb and dorsum of the left hand. He was a native of Michigan and had recently moved to California because of "lung trouble." The family history was unimportant excepting that one brother had died of tuberculosis and that the patient had cared for him during the last three months of his illness. His general health had been good until May, 1910, and he had worked in a grain elevator where there was a great deal of dust. His illness began with a cough and with sharp pain in the right side of the chest. The cough became progressively worse, there was much thick, blood-stained sputum, and finally there was spontaneous hemoptysis without coughing. The patient said that tubercle bacilli had never been found in the sputum.

He was "sick all summer," had anorexia, nausea and vomiting, high fever in the afternoons, frequent night sweats, dyspnea, progressive weakness, rapid pulse rate and rapid loss of weight. After coming to California he improved in general health, the cough disappeared and he was able to work as a farm laborer.

In March, 1911, he noticed a "pimple" on the back of the thumb which became pustular and discharged a small amount of pus. A small ulcer formed which progressively enlarged in all directions. In May a similar nodule appeared on the same thumb, and it also resulted in the formation of a progressively enlarging ulcer. There were burning and itching in both lesions, but there was never any pain. In October, 1911, the lesions were examined by Dr Ophuls, who gave the following report: "Large superficial ulcer on extensor surface of thumb and another on the adjoining part of the hand. Ulcer on thumb covers practically the entire extensor surface, the other is round, about 3.5 cm in diameter. The floor of the ulcers is rough, somewhat papillary, and covered with crust. The edges are elevated. At the edges and on the floor of the ulcers are milium abscesses which discharge pus on pressure. In the pus are many flat, horny epithelial cells and a moderate number of spherical fungi with double-contoured capsules, some of which show budding."

The patient continued in fair health and was able to work until the latter part of January, 1912, when he was kicked in the back by a horse. A short time later he noticed a pain in the left lumbar region which became more severe until there was sharp, throbbing pain which extended into the left groin, the region of the bladder and the left testicle. The pain was paroxysmal and occurred mostly at night. There was frequent urination. Examination showed tenderness in the region of the left kidney and a few red blood corpuscles in the urine. The pain and disability became worse until the patient was forced to remain in bed, and frequent hypodermic injections of morphin were necessary. Soon a septic type of temperature and evidences of an abscess in the region of the left kidney developed. Operation was performed and a large perirenal abscess was drained, but the patient did not recover sufficiently to

leave his bed. He became very much emaciated, developed a severe cough, had much sputum and numerous night sweats. The temperature remained septic in type. The sinus from the perirenal abscess continued to discharge, and the patient constantly suffered from very severe pain. He died, June 13, 1912.

At necropsy, the second and third lumbar vertebrae were found to be almost completely destroyed, and they were replaced by a large abscess cavity. There were a few small cavities in the lungs and a few small abscesses in the subcutaneous tissues of the arms. There was no complete record of the necropsy findings, and no bacteriologic or histologic examination was made of the materials obtained.

In closing, I wish to express my thanks to Professor Ophuls for permission to use the records of the Division of Pathology, and to the various gentlemen mentioned in the protocols for their courtesy in sending me the clinical records of their cases.

CONCLUSIONS

1 Cases of coccidioidal granuloma have occurred with sufficient frequency to establish the disease as a clinical entity.

2 The condition so closely resembles tuberculosis as to be practically indistinguishable unless the characteristic parasite is recognized.

3 It is probable that many cases are diagnosed tuberculosis, and that if routine examination for the parasite were made in cases which are clinically tuberculosis but in which the tubercle bacillus cannot be found, the number of recognized cases of coccidioidal granuloma would rapidly increase.

4 Coccidioidal granuloma and blastomycosis, though closely related, are etiologically distinct.

5 Although the great majority of cases of coccidioidal granuloma prove fatal the progress of the disease may be prevented in a few cases by radical removal of the infected parts.

6 A very small proportion of the cases may undergo spontaneous recovery.

A CASE OF ACUTE MILIARY TUBERCULOSIS

SHOWING THE BLOOD PICTURE OF AN ACUTE MYELOGENOUS LEUKEMIA

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The case I report came under my observation Nov 21, 1914, one month after the beginning of the illness. The following history was obtained from the attending physician, Dr William Blair

Mrs B, a housewife, aged 52, had an unimportant family history except her mother died of cancer. There was no history of tuberculosis in any branch of the family. With the exception of a rather severe rheumatic fever nineteen years ago, the patient has been unusually strong until the beginning of the present trouble. This began one month ago with a feeling of unusual fatigue and slight fever. The elevation of temperature has continued to the present time and has been irregularly remittent ranging from normal to 101.8. There have been chilly sensations at times but never a definite rigor. On Oct 27, 1914, two days after the beginning of the illness, the blood count was as follows: erythrocytes, 3,000,000, leukocytes, 16,480, hemoglobin, 85 per cent (Sahli)

Physical Examination—Oct 21, 1915. This showed a medium-sized woman stuporous for the most part but showing irritability when disturbed. Temperature 101.8, pulse 116, respiration 26. There was a marked pallor of the mucous membranes. The skin was manifestly anemic but showed a slight cyanosis as well as a decided icteroid tint similar to that which characterizes pernicious anemia. Panniculus adiposus was abundant, strikingly so in view of the advanced severe anemia and marked toxemia. There were no glandular enlargements. The eyes followed the moving finger poorly owing to difficulty in maintaining attention. The pupils were equal and reacted both to light and accommodation. There was no rigidity of the neck muscles. Knee-jerks were exaggerated. Babinski and Kernig negative. There was a marked ankle clonus. The heart and lungs were negative. The liver was distinctly palpable almost a breadth below the costal margin but was not tender. The spleen was palpable. The abdomen was tympanitic throughout, not distended and not tender. The blood findings on the above date were the following: erythrocytes, 1,320,000, leukocytes, 23,840, hemoglobin, 20 per cent (Sahli)

On account of the prolonged irregular temperature with a leukocytosis, rapidly progressing anemia and the absence of signs of any localized disease a provisional diagnosis of streptococcus septicemia was made. A blood culture made on the above date with alkaline bouillon gave negative results, however.

November 23. The maximum temperature was 101.4. There was increasing weakness and cyanosis, and breathing was somewhat labored. The urine showed a trace of albumin and a large number of casts. Hemoglobin, 15 per cent (Sahli), leukocytes, 13,000.

November 24. The urine contained a trace of albumin and a very few leukocytes but was negative for Bence-Jones bodies.

November 26. Maximum temperature 100.4 F. There was definite improvement of strength and more marked stupor.

November 28 The patient complained of air hunger which steadily increased during the day Was somewhat relieved by lowering the head, bandaging the legs and administering oxygen

November 29 Air hunger greatly increased Pulse 150 Respiration 50 Patient died, apparently an anemic death, the air hunger being the most striking feature for the last twenty-four hours of life

A differential count made two days before the patient's death gave the following results Polynuclear leukocytes, 42.5 per cent, lymphocytes, 4 per cent, large mononuclears, 18.5 per cent, myeloblasts, 2.4 per cent, premyelocytes, 1.8 per cent, myelocytes, 30.4 per cent, the total myelocytic forms being 34.8 per cent, 2 nucleated reds were found in the one preparation

The necropsy report by Dr A. S. Warthin was as follows

Nov 29, 1914 Pathological Diagnosis Primary tuberculosis of bronchial nodes Healed tubercle in right lung Miliary tuberculous focal necroses in lung, liver, spleen and bone marrow Cold abscesses in bronchial nodes, secondary pyogenic infection, rupture of abscess into pulmonary vein Older miliary tubercles in kidney Tubercle bacilli colonies in myocardium Exhaustion of bone marrow Secondary anemia gravis aplastica, so-called Chronic fibroid salpingitis Fatty degeneration of heart and liver Multiple thromboses in pulmonary veins, portal vein and ovarian plexus

General External Examination Build slender, body length 162 cm Body bloodless, small amount of blood in veins Mammæ atrophic No nodules in breast Cervical and axillary nodes not palpable, inguinal just palpable Splenic dulness does not extend below edge of ribs

Eyes Conjunctiva of slight lemon color

Thorax Somewhat depressed Epigastric angle less than right angle Moderate corset thorax

Abdomen Below level of ribs Negative on palpation

Skin Pale, translucent, brunette, more pigmentation over face and flexor surfaces Pigmented moles over face, shoulders and neck, some paler with no pigment

Teeth Those remaining are in bad condition, a number are false

Mucous Membranes Pale, bloodless Gums pale — no lead line

Rigor Mortis In chin and hands Absent in feet and legs

Panniculus Abundant

Edema Moderate in lower extremities, trace throughout body

Hypostasis Pale

Ears Negative

Genitalia Negative

Thorax and Abdomen (main incision) Panniculus Pale yellow, with coarse lobules, almost bloodless, moist, shining

Musculature Bright, shiny, red, as in carbon monoxid poisoning

Omentum Shows small amount of fat

Position of Abdominal Organs Spleen extends to edge of ribs Liver is hand's breadth below ensiform, finger's breadth below ribs

Mammæ Right atrophic, shows small amount of tissue, mostly fat Left shows more gland tissue

Costal Cartilages Cut easily, except first on left, which is calcified Sternum moderately osteoporotic, shows no thickening of periosteum

Thorax No fluid in left pleural cavity, about 300 c c of clear fluid in right Lungs free, distinct, firm nodules back of suprasternal notch Apex of heart behind fifth rib in left parasternal line

Anterior Mediastinum Mediastinal fat lemon yellow

Thymus Thymic fat is firm and replaced by definite firm nodules On section shows hyperplastic lymph nodes — firmer and more translucent than normal

Pericardium Pericardial tension not increased Fluid increased and blood-tinged Small patches of recent pericarditis

Heart Flabby, smaller than cadaver's fist Large soldier spot over anterior wall of right ventricle Small amount of blood in great vessels Auricles collapsed, contain pale clots and small amount of blood Fatty degeneration of muscle of right ventricle Right ventricle measures 7 mm, 4 mm of which is fat Left ventricle measures 12 mm, fatty degeneration of muscle Mitral valve admits three fingers, flaps negative Tricuspid valve admits three fingers

Left Lung Airless, filled with pin-point and larger nodules, a conglomerate nodule, size of cherry On section, lung shows edema, congestion and numerous miliary nodules, not caseating, translucent, firm, rising above surface, and more red than tubercles

Right Lung Heavy Pleura shows numerous white, firm nodules—most marked on posterior surface Largest nodule is size of a cherry, umbilicated, in upper lobe On section it is seen to be an encapsulated, caseated tubercle Lung on section shows marked edema and everywhere miliary tubercles of all sizes, none showing caseation

Neck Trachea Bronchial glands enormously enlarged—size of small orange—surround trachea, which on section show multiple abscess cavities containing greenish pus Abscess wall is smooth, covered with creamy gray material—no sulphur granules visible In a gland whose structure is preserved there are no distinct tubercles Thyroid slightly enlarged, abundant colloid

Abdomen Peritoneum Moist, shining throughout

Spleen Not adherent, large, firm Shows small miliary nodules through capsule On section is seen to be completely strewn with miliary nodules, raised Two of the larger nodules on scraping show central softening

Large Intestine Transverse colon shows W fold descending to pelvis Descending colon and cecum filled with soft gray feces and gas No neoplasm in any part of intestinal tract

Appendix Adherent to ovary, broad ligament and bladder, buried in fat, 3 cm long, lumen partially obliterated—old chronic obliterative appendicitis

Duodenum Shows slight brownish mucus

Stomach Empty Fundus contains about a pint of fluid and gas Mucosa of stomach very pale, smooth Mucosa of fundus atrophic No neoplasm

Pancreas Shows normal firmness, pale Lobules normal Nothing pathologic

Liver Moderately large, edges fairly sharp Capsule thick near ligaments Over entire surface are numerous miliary nodules of all sizes Upper pole shows hemangiocavernosum 30 by 20 mm On section liver is pale, chocolate-brown, lobules slightly smaller than normal Cloudy, opaque, innumerable nodules from pin-point to mustard seed in size, without caseation

Gallbladder Empty, opaque, long, pendulous, thick

Left Adrenal Normal in size In medulla are nodules pin-head in size, firm, hyaline, without caseation

Kidneys Left Fatty capsule abundant Fibrous capsule strips easily Surface smooth Shows slight traces of fetal lobulations Same kind of nodules as seen elsewhere Cut surface is pale, cortex atrophic, parenchyma cloudy. Pelvis negative Ureter negative Right kidney resembles left in every way Retroperitoneal lymphnodes are hyperplastic

Pelvis No neoplasm in pelvis Rectum negative

Bladder Distended On section, mucosa otherwise negative

Uterus Hard, fibrous, but no neoplasm Uterus small Endometrium very atrophic Cervix shows old lacerations, catarrh Right tube and fimbriated appendage adherent to appendix and cecum Cecum and tube are stretched Ovaries show fibroid atrophy, more marked in right

Special Regional Examination Ribs and vertebrae are negative, the marrow is very dry, exhausted

Microscopic Findings Lungs Miliary areas of coagulation necrosis containing colonies of tubercle bacilli. A few show beginning tubercle formation. Marked edema. Nodule in right lung is an old hyaline, calcified, healed tubercle. No active tubercles about it.

Bronchial Nodes Multiple cold abscesses. Tubercles with secondary infection. Large caseous tubercles.

Heart Old scleroses of epicardium. Fatty infiltration of epicardium with serous atrophy. Marked fatty infiltration of heart muscle. Fatty degeneration of muscle with atrophy. Small areas of leukocyte infiltration in the myocardium—localization of tubercle bacilli. Sclerotic patches in endocardium. Marked fatty degeneration and Zenker's necrosis of papillary muscle. Clots from heart are white, containing few red blood cells but enormous numbers of atypical nucleated cells resembling myeloblasts, atypical myelocytes and bone-marrow lymphocytes.

Liver Multiple focal necroses, coagulation and caseation. Numerous localized collections of lymphocytes. Tuberculous thrombus in portal vein branches. Some few lesions show beginning tubercle formation, but the majority are the primitive lesions produced by tubercle bacilli. When stained for tubercle bacilli these areas show pure colonies of bacilli. Acute passive congestion and fatty degeneration.

Spleen Acute passive congestion. Multiple foci of coagulation and caseation necrosis containing pure colonies of tubercle bacilli. No fully developed tubercles.

Kidneys Cloudy swelling. Acute passive congestion. Atrophy. Dilatation of tubules. Numerous hyaline glomeruli. Few miliary tubercles, older and larger than lesions in lung, liver and spleen. Adrenals, fatty degeneration. Atrophy. No tubercles.

Cervix Cervical catarrh and cystic glands, endometrium, atrophic. Fallopian tubes, chronic fibroid, healed salpingitis. Ovary, hyaline laminated thrombus in ovarian plexus.

Bone Marrow Exhaustion of red-cell forming marrow. Small points of coagulation and caseous necrosis in the marrow. Numerous atypical myelocytes and myeloblasts.

Before discussing this very unusual leukocyte picture, it would be well to consider the blood findings which usually obtain in acute miliary tuberculosis, as well as in other forms of tuberculous infection. Until within the last few years very little attention was paid to the differential leukocyte count as a possible means of differential diagnosis in those infections, characterized by normal or diminished total leukocyte counts, of which typhoid fever and acute miliary tuberculosis are the most frequently encountered examples.

Steffen,¹ in his researches on the blood findings in pulmonary tuberculosis, demonstrated that at least in cases making favorable progress there is a marked relative lymphocytosis, and any increase that may occur in the polynuclear elements he ascribed to the beginning of a secondary infection. It has been quite generally accepted that the tubercle bacillus, occurring alone, calls into action only the lymphoid elements of the blood inasmuch as tubercle formation requires

¹ Steffen. Ueber Blutbefunde bei Lungentuberkulose, *Deutsch Arch f klin Med*, 1910, cxiii, 355.

only these elements, in addition to the epithelial and giant cells, for its consummation, the leukocytes playing no part whatever in this process Mathes,² however, has shown that in uncomplicated miliary tuberculosis, a condition in which the possibility of secondary infection can be more easily ruled out than in pulmonary tuberculosis, it is the rule to find a relative increase of the polynuclears with a corresponding decrease in the lymphocytes, the total count varying from normal to a rather marked leukopenia. This work of Mathes has been recently verified by Wack³ of the Marburg clinic who reports seven cases of acute miliary tuberculosis with differential blood counts. He makes the very interesting observation that at the beginning of the illness there may be little if any reduction in the number of lymphocytes but, as the disease progresses, there is a gradual diminution in the number to as low as 3 or 4 per cent with a total count of 5,000 and 6,000. Nägele⁴ has shown that in typhoid fever, on the other hand, particularly in its late stages with severe leukopenia, the lymphocytes are relatively increased and may comprise one-half of the white blood cells.

In meningeal tuberculosis where one usually finds a slight or moderate leukocytosis, Wack finds that here, also, the increase affects only the polynuclears, the lymphocytes remaining unchanged or decreased in number according to the stage and severity of the disease just as was found in uncomplicated miliary tuberculosis. On the contrary, in all other forms of meningitis while there may be only a moderate leukocytosis, the lymphocytes as well as the polynuclears are increased in number.⁵

Turning now to my own case, we find, first of all, instead of a leukopenia, a rather marked leukocytosis, the minimum count being 13,000, the maximum 23,000. *A priori*, this would suggest either a secondary infection or perhaps an accompanying tuberculosis meningitis. The latter, while not ruled out by a postmortem examination of the central nervous system, can, I think, be excluded as a cause for the leukocytosis, for the increased white count was noted very early in the course of the infection, three days after the beginning of the illness. Had this marked the beginning of a meningitis surely some clinical evidence of meningeal irritation would have developed within a period of five weeks. If one should regard the suppurating bronchial nodes as the cause for the increased leukocyte count, one

2 Mathes Die Diagnose der Miliartuberkulose, Med klin, Breslau, 1912

3 Wack, P Ueber Leukocytenbefunde bei Miliartuberkulose und ihre diagnostische Bedeutung, Deutsch Arch f klin Med, 1914, cxv, 596

4 Nägele Blutkrankheiten und Blutdiagnostik

5 Rusca Das Blutbild der Meningitis Cerebrospinalis epidemica und dessen diagnostische und prognostische Bedeutung, Deutsch Arch f klin Med, 1911, ciii, 235

would still be left without sufficient pathology to account for the striking changes in the differential count. On the other hand, the miliary tuberculosis in this case showed an unusually extensive dissemination, a remarkable number of bacterial foci showing only the coagulation necrosis of recent bacillus localization. The unusual virulence of the tuberculosis furnishes the only satisfactory explanation for the appearance of immature leukocyte forms in the blood stream. There was certainly no general septic process, for the blood was found to be sterile seven days before death and there were no metastatic septic foci found at necropsy.

We are dealing, therefore, with a comparatively simple clinical factor inasmuch as there existed no such complication as might be expected to produce striking modifications in the leukocyte production. In view of the postmortem findings, therefore, this blood picture was a very unusual one. In addition to there being a large number of immature forms of leukocytes, there were striking deviations from the accepted morphologic standards of the various types of leukocytes. This was true to such an extent that many of the cells were difficult to classify. All forms were very poorly granulated. Many of the polynuclears were entirely without granules, as were also many of the myelocytes. Granulation, therefore, could not be used as a means of identification. This lack of granules often resulted in a striking similarity between certain of the more mature myelocytic forms and the large mononuclears. The relative size of the nucleus, its structure and staining properties was, therefore, made the basis of differentiation, particular attention being paid to the maturity of the nucleus. While the classification adopted might be looked upon as rather arbitrary, it is nevertheless one that purposely avoids controversial questions. All nongranular cells with a homogeneous basophilic cytoplasm and a round or oval deeply staining structureless nucleus, were classed as lymphocytes regardless of size. All cells with relatively large faintly staining oval or indented vesicular nuclei, were classed with the myelocytic forms. All mononuclear forms larger than a normal polynuclear, showing relatively small well-matured nuclei, were designated as large mononuclears regardless of the shape of the nuclei, and I may say that practically all the cells placed in this group correspond to the *Macroleukoblasten* (*pathologische Monocyten*) of Pappenheim.⁶ With no desire to favor any one of the various theories of leukocyte development or to advocate any one system of nomenclature, the writer

6 Pappenheim, A. Atlas der Menschlichen Blutzellen, 1905. Unsere derzeitigen Kenntnisse und Vorstellungen von der Morphologie, Genese, Histogenese, Funktion und diagnostischen Bedeutung der Leukocyten, Ergebn d inn Med und Kinderh, 1912, viii, 183.

has, however, as a matter of convenience and uniformity, adhered to Pappenheim's classification and terminology

Some unusual myelocytic forms were observed, that is, there were some showing deeply lobulated nuclei and others with larger horse-shoe shaped nuclei resembling that of the so-called transitional cell except the nuclear structure was very immature, being faintly stained, more or less homogeneous and vesicular in appearance. The polynuclears were very poorly developed, being almost entirely nongranulated, and rarely were the nuclei divided. There were no eosinophils. The red cells showed very little change, considering the severity of the anemia. Only two nucleated forms were found in any one preparation. The cells reacted to the stain uniformly and there was practically no poikilocytosis or anisocytosis.

This case is a particularly interesting one when viewed purely from the clinical standpoint, for inasmuch as it presented no positive diagnostic points either in the history or in the physical examination, the striking blood picture immediately became a point of unusual interest and was naturally looked on as holding the key to a positive diagnosis. Obviously the question of a possible acute leukemia was the first to command attention. With the unusual number of immature forms and with numerous atypical forms of the various ages of leukocytes, acute leukemia could not be ruled out. The short course of the disease together with the severe anemia would also favor the diagnosis of acute leukemia or more nearly, perhaps, that poorly defined clinical entity leukanemia. In fact, some of the reported cases of acute leukemia have shown a percentage of myelocytic forms no higher than the case under discussion. Neither does the absence of a very high leukocyte count speak against such a conception, for a number of cases of acute leukemia have been reported in which there was no increase in the leukocytes.

Quincke,⁶ Nana, Dock⁷ and Warthin have reported cases of chronic myelogenous leukemia, complicated by acute miliary tuberculosis in which, during the course of the terminal tuberculosis, the leukocyte count dropped to normal and some of the reported cases showed at necropsy complete disappearance of the myeloid changes. The case under discussion would scarcely fall into this class for there had been no such previous ill health as would suggest a chronic leukemia. In this case, therefore, the absence at necropsy of all leukemic changes and the finding of an uncomplicated miliary tuberculosis leaves us with

⁷ Quincke. Leukämie und Miliartuberkulose, *Deutsch Arch f klin Med*, 1902, lxxiv, 445

⁸ Dock. *Am Jour Med Sc*, 1904, cxlvi, 563

only the tuberculosis to account for the peculiar leukocyte picture. The latter, since it is not in accordance with the usual leukocyte finding in milary tuberculosis as shown by the researches of Mathes and Wack, would, I believe, have to be looked on as due to a peculiar susceptibility of the individual. One need not regard the peculiar reaction of the myeloid tissue in this instance, in the light of a specific response to some peculiarity in the infecting organism, for this tendency for immature forms to appear in the circulating blood has been frequently observed in infections with such other organisms as the pneumococcus and streptococcus, and has been regarded as a manifestation of very poor resistance on the part of the infected individual. Why should not the same thing occur in infections with the tubercle bacillus, an organism which possesses in common with the pneumococcus and streptococcus the power of calling forth neutrophil polynuclears in relatively if not in actually increased numbers? That such a leukocyte picture should be found very rarely in infections with the tubercle bacillus as compared with infections with the streptococcus and allied organisms, is only in accordance with the hypothesis and should not constitute a reason for seeking some other explanation of the phenomenon. To be sure one would have to consider the possibility of an extension of the tuberculous process into the bone marrow, leading to destruction of a portion of the marrow and an abnormal activity of the remaining portion. This condition, however, was not found at necropsy.

On searching the literature for similar cases, one finds a report by Otto Roth⁹ of a case of subacute milary tuberculosis with the blood finding of a myeloblastic leukemia. A woman 50 years of age died of a subacute illness characterized by fever, swelling of the lymph glands, a severe anemia and a hemorrhagic tendency. The differential leukocyte count was as follows: Neutrophil polynuclears, 36 per cent, premyelocytes, 22 per cent, neutrophil myelocytes, 13 per cent, myeloblasts, 76.6 per cent, eosinophils, 0.1 per cent, lymphocytes, 15.6 per cent. Large mononuclears and transitionals, 0.6 per cent.

Necropsy showed a subacute milary tuberculosis with recent septic foci in the spleen and parotids (staphylococcus infection). I am indebted to Roth for the review of the literature of the subject prior to 1913. Kast¹⁰ reports a case in a child 15 months old with advanced tuberculosis of the bronchial glands and upper lobe of the left lung, as well as milary tuberculosis of the liver, spleen and kidneys (bone

9 Roth, Otto. Ueber einen bemerkenswerten Blutbefund bei einem Fall von sub-akuter Milartuberkulose, *Ztschr f klin Med*, 1913, lxxviii, 75.

10 Kast. *Med Klin*, Breslau, xviii. Referred to in *Munchen med Wchnschr*, 1902, xlix, 2093.

marrow normal) The case presented a peculiar form of leukocytosis which led to the diagnosis of leukemia Myelocytes, 31 per cent , polynuclear leukocytes, 32 per cent , eosinophil cells, 7.5 per cent , lymphocytes, 17 per cent , large mononuclear and transitional forms, 2 per cent ; and mast cells 10.5 per cent Case 18 of von Mullern and Grossmann,¹¹ also reviewed by Roth is a similar case A child 5 years old died, after a short illness, of fever with hemorrhagic tendencies, with the blood findings of an acute myelogenous leukemia Necropsy showed subacute and acute tuberculosis of the lymph glands and myelogenous metaplasia in the spleen and liver Roth also includes Bruchmann's¹² case in this class (tuberculosis of the lymph glands and of the peritoneum together with myelogenous leukemia in a boy 13), and Masing's (a man of 20 with "leukemia") necropsy showing tuberculous nodules in the lungs and pleura, also tuberculosis of the bronchial glands Leube's¹³ case, which gave rise to the conception of leukanemia when viewed in the light of more recent studies of the blood changes in severe infectious processes, would have to be regarded as a case of general sepsis with an unusual functional leukocytosis His case was a boy 4 years old who died from a high fever after a short illness There was a severe anemia (hemoglobin 10 per cent) and a differential leukocyte count as follows neutrophils, 44.1 per cent , neutrophil myelocytes, 13 per cent , eosinophils, 0.6 per cent , large lymphocytes, 4.9 per cent , small lymphocytes, 35.3 per cent Necropsy showed a septic tumor of the spleen with central abscess and small abscesses in the liver

Hertz¹⁴ regards the majority of the reported cases of acute myelogenous leukemia as cases of severe infection He holds that there is no uniform etiology but that various infectious centers are capable of producing such a blood picture An unusual susceptibility on the part of the individual, no doubt, is also an important factor This same tendency in a minor degree is a matter of common observation in various infectious processes, manifesting itself by the appearance in the blood stream of a few myelocytes The deviation of the Arneeth count to the left is a manifestation of this same tendency and while it is only a feeble manifestation, it is, nevertheless, regarded as a true expression of the ratio between the strength of the invading organism on the one hand and the resistance of the individual on the other

11 Von Mullern and Grossmann Beitr z path Anat u z allg Path, 1912, 11 Reviewed by Roth in Ztschr f klin Med, 1913, lxxviii, 75

12 Bruchmann Ein Fall von Lymphdrusen und Bauchfelltuberkulose usw, Arbeiten aus dem patholog, Anatom Institut zu Tubingen, 11, Part 3

13 Leube Sitzungsber d phys med Gesellsch, Murburg, 1900

14 Hertz Die Akute Leukamie, Wein, 1911

A study of this case and a review of similar cases in the literature leads to the conclusion that many of the so-called cases of acute leukemia are, after all, only cases of infection, presenting unusual leukocyte pictures

The writer wishes to express his appreciation of the kindness of Dr A S Warthin in contributing the very complete necropsy report

THE URIC ACID SOLVENT POWER OF URINE CONTAINING HEXAMETHYLENAMIN (UROTROPIN) AS COMPARED WITH THAT OF NORMAL URINE *

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It has been known for a long time that hexamethylenamin in aqueous solution has the power of putting into solution considerable uric acid. In illustration of this point we take occasion to report one of our own experiments. An excess of pure uric acid was added to five solutions of hexamethylenamin, and after being shaken they were kept in an incubator at body temperature over night. The uric acid in the filtrates from these was estimated by the usual method, the results being as follows:

35.00 mg	of uric acid dissolved by 100 c c	of 0.1 per cent
66.00 mg	of uric acid dissolved by 100 c c	of 0.25 per cent
74.00 mg	of uric acid dissolved by 100 c c	of 0.4 per cent
158.00 mg	of uric acid dissolved by 100 c c	of 2.0 per cent
250.80 mg	of uric acid dissolved by 100 c c	of 5.0 per cent

The solubility of uric acid in distilled water under the same conditions is about 8.4 mg. From these findings it is easy to understand how the claim could be made that hexamethylenamin exerts a marked uric acid solvent action. It is necessary, however, to mention parenthetically, that such concentrations as these are greater than can occur in the urine after administration of therapeutic doses.

When we investigate the behavior of urines containing hexamethylenamin we find that many of them possess no power to take up uric acid in addition to that already present, while, on the other hand, many do show a marked solvent power. The investigation reported in this paper has shown that those hexamethylenamin urines which possess a distinct uric acid solvent power are the ones which have the same acidity reaction as those normal urines that have the ability to dissolve uric acid in appreciable quantity. It became necessary, therefore, to make an extended study of the action of normal urines¹ in dissolving uric acid, and then to compare the results with those obtained with

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1 It is the author's intention to give all the data for normal urine quite fully in a separate paper.

urines containing the drug. It seems quite possible that by means of this comparison the present research has settled the question of the uric acid solvent power of hexamethylenamin.

METHODS

The uric acid estimations were made by the usual method, *i. e.*, by precipitation by means of ammonium hydroxide in the presence of a considerable concentration of ammonium sulphate, filtration and subsequent solution of the precipitate in hot dilute sulphuric acid and its estimation by titration with a standard solution of potassium permanganate.

In determining solvent power the urines were first warmed to 37 C, and after adding an excess of pure uric acid the flasks were kept in a bath at 37 C for exactly twenty minutes, the urines being shaken frequently so that undissolved uric acid was constantly in suspension. They were filtered immediately after removal from the bath, and the uric acid estimation was made on the filtrates. A longer period of warming and shaking was not found to give superior results. Body temperature was chosen so as to be comparable to the physiological condition of urine lying in the bladder.

The hydrogen-ion concentration or acidity of the urine was determined by the method of Henderson and Palmer². Without this method the research could never have been satisfactorily carried out. The figures in the tables for acidity of the urines are the "hydrogen exponents", these are really (negative) logarithmic figures corresponding to the true hydrogen-ion concentrations. The smaller the figure the greater the acidity. Exact neutrality is 7.0. The reaction of the normal urines which we have examined ranges from a distinctly acid urine, 5.0, to a slightly alkaline urine, 7.4, never quite equalling the alkalinity of blood which is 7.45 to 7.65.

The most puzzling part of the work was to discover the factors which control the solvent action of normal urine on uric acid. The only factors which we have definitely proved to play a part are the acidity and the concentration of the urine. As to the effect of the acidity, it was found that practically all urines, 6.5 to 7.4, are able to take up additional uric acid, and that a certain proportion of more acid urines, 6.2 to 6.45, dissolve some uric acid, but very few of those, 5.8 to 6.1, have any effect. The amount of uric acid dissolved corresponds roughly to the reaction, increasing as the acidity lessens. As regards the other factor, namely, concentration of the urine, it was a surprise to find that many dilute urines dissolve a disproportionately large amount of uric acid. One might naturally suppose that a 50 per cent dilution of a particular urine would dissolve about half as much as the undiluted urine, but as a matter of fact it dissolves much more than that. In consequence of this in the tables below dilute hexamethylenamin urines are compared with dilute normal urines, and the less dilute with less dilute controls.

We had great difficulty in securing a sufficient number of samples of urine, both normal and drug-containing, of low enough acidity to show uric acid solvent power³. This was especially true in summer (at which time most of the work had to be done), since on hot days almost every sample of urine passed proved to be too acid to dissolve uric acid.

² Henderson, L. J., and Palmer. *Jour Biol Chem*, 1913, **xiii**, 393.

³ The author wishes to express his indebtedness to the large number of students and others who have furnished urines for this research, but most of all to Dr. P. J. Hanzlik and R. J. Collins, who secured the samples of hospital urines as well as other urines. They also made most of the tests for hexamethylenamin. The assistance of C. J. Friedman in the research was invaluable.

It may be postulated as a necessary condition to be able to claim that a particular urine dissolves more uric acid than the same urine with hexamethylenamin, such a urine must take more than do normal urines of corresponding acidity. Only on this basis can we determine that the amount excreted in the urine is a factor in the uric acid index.

The tables give the results of the experiments, serving as controls for comparison. The amount given as milligrams in 100 c c of urine is the amount present in the urine as passed. The amount present in the filtrate after shaking is the difference between these two is the "uric acid index" or index of the solvent power of the urine. In giving the controls the columns are arranged so as to bring the figures for "uric acid dissolved" and "uric acid" in comparison. As regards the dosage of hexamethylenamin, a dose was taken by the normal individuals when two doses of 2 gm were taken (2 gm each). In the cases the time interval for secretion of the drug was the time of taking the last dose. The drug was given in doses, but the hospital patients took the drug 3 times per day or the hours between doses were 4 tables.

COMMENT ON THE

It may be objected by some that in the cases above, the time interval for secretion of the drug after the administration of hexamethylenamin is not more than a trace of the drug. According to P. J. Hanzlik, however, after giving a single dose of hexamethylenamin gives a distinct test as early as twenty minutes in some of the cases and inside of thirty-five minutes in the cases.

On studying Table 1 we find that the amount of uric acid in most of the drug urines is no greater than in the normal urines. In some cases a few milligrams in excess, but in no case a notable excess of uric acid dissolved (normal range 63—65 mg) and acidity 63—65 mg. In the first of

TABLE 1—URINES CONTAINING HEXAMETHYLLNAMIN—
DILUTE URINES OF NORMAL PERSONS

Acidity	Dosage gm	Time Hours	Hexam Test	Uric Acid Content mg	Total Uric Acid mg	Uric Acid Dissolved mg
72	20	0 -1	+	31 65	178 69	147 04
72	20	0 - $\frac{3}{4}$	+	17 92	88 88	70 96
695	20	0 -6	+	8 96	77 78	68 82
675	20	1 -1 $\frac{3}{4}$	+	7 48	48 92	41 44
67	20	1 $\frac{3}{4}$ -2 $\frac{3}{4}$	+	8 22	88 14	79 92
67	20	$\frac{1}{4}$ - $\frac{1}{2}$	+	7 48	77 04	69 56
67	20	5 $\frac{1}{2}$ -6	+	8 96	68 96	59 94
66	20	2 $\frac{3}{4}$ -4	+	8 96	114 04	105 08
66	20	4 -5	+	17 92	97 84	79 92
66	20	3 $\frac{1}{4}$ -4	+	9 70	61 50	51 80
65	20	4 -5 $\frac{1}{2}$	+	26 80	96 36	69 56
65	20	1 -2 $\frac{1}{2}$	+	19 40	87 40	68 00
645	20	2 $\frac{1}{2}$ -3	+	8 96	46 70	37 74
645	20	$\frac{1}{2}$ - $\frac{3}{4}$	+	7 48	42 26	34 78
645	20	$\frac{3}{4}$ -1	+	8 22	38 56	30 34
64	2 \times 2	0 - $\frac{1}{2}$	+	10 44	62 24	51 80
635	20	2 $\frac{1}{2}$ -3	+	9 70	34 86	25 16
635	20	$\frac{1}{4}$ - $\frac{1}{2}$	+	7 48	32 64	25 16
63	2 \times 2	2 $\frac{1}{2}$ -4	+	32 64	97 76	65 12
63	10	0 - $\frac{3}{4}$	+	20 88	37 16	16 28
63	20	$\frac{1}{2}$ -1	+	7 48	31 16	23 68
61	2 \times 2	$\frac{1}{2}$ -2 $\frac{1}{2}$	+	18 58	60 76	42 18
61	20	1 $\frac{1}{2}$ -2 $\frac{1}{2}$	+	14 88	37 24	22 36
61	10	0 -2	+	9 70	33 38	23 68
585	20	1 $\frac{1}{2}$ -2	+	8 22	11 18	2 96
58	20	2 $\frac{1}{4}$ -4	+	20 88	25 24	4 36

TABLE 2—

LESS DILUTE URINES OF NORMAL PERSONS

725 *	10	$\frac{3}{4}$ -3	+	78 71	335 85	257 14
72	10	$\frac{3}{4}$ -3 $\frac{1}{2}$	+	37 08	161 40	124 32
71	10	$\frac{1}{2}$ -4 $\frac{1}{2}$	+	43 00	176 94	133 94
595	10	0-3 $\frac{1}{4}$	+	47 52	51 88	4 36

TABLE 3—

URINES OF DISPENSARY PATIENTS

72	20	$\frac{3}{4}$ -1 $\frac{3}{4}$	+	16 40	102 80	86 40
665 *	20	0 -1	+	18 40	87 50	69 10

URINES CONTAINING NO HEXAMETHYLENAMINE	DILUTE NORMAL URINES
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
12	12
13	13
14	14
15	15
16	16
17	17
18	18
19	19
20	20
21	21
22	22
23	23
24	24
25	25
26	26
27	27
28	28
29	29
30	30
31	31
32	32
33	33
34	34
35	35
36	36
37	37
38	38
39	39
40	40
41	41
42	42
43	43
44	44
45	45
46	46
47	47
48	48
49	49
50	50
51	51
52	52
53	53
54	54
55	55
56	56
57	57
58	58
59	59
60	60
61	61
62	62
63	63
64	64
65	65
66	66
67	67
68	68
69	69
70	70
71	71
72	72
73	73
74	74
75	75
76	76
77	77
78	78
79	79
80	80
81	81
82	82
83	83
84	84
85	85
86	86
87	87
88	88
89	89
90	90
91	91
92	92
93	93
94	94
95	95
96	96
97	97
98	98
99	99
100	100

CONTROLS		URINES CONTAINING NO URIC ACID		DILUTE NORMAL URINES		Remarks
Uric Acid Dissolved mg	Total Uric Acid mg	Uric Acid Content mg		Acidity		
144.75	154.50	9.75		7.3		
157.29	172.25	14.96		7.1		
118.40	138.80	20.40		7.0		
105.66	122.16	16.50		6.95		
69.60	78.00	8.40		6.95		
83.00	91.25	8.25		6.75		
57.20	66.00	8.80		6.75		
96.75	105.00	8.25		6.7		
66.38	81.91	15.53		6.7		
61.50	69.00	7.50		6.6		
75.75	83.25	7.50		6.6		
74.41	78.12	3.71		6.5		
63.00	72.00	9.00		6.5		
63.92	76.16	12.24		6.45		
50.80	66.00	15.20		6.45		
51.48	59.04	7.56		6.45		
33.60	41.20	7.60		6.4		
32.80	55.60	22.80		6.4		
48.75	68.40	19.65		6.35		
31.20	38.80	7.60		6.35		
22.94	30.42	7.48		6.3		
5.60	14.00	8.40		6.3		
33.75	41.25	7.50		6.25		
19.20	31.60	12.40				
19.50	27.06	7.56				
				14.42		6.0
				10.00		6.0
				10.68		5.95
				9.20		5.8
	52.33					
	22.00					
	25.50					
	29.20					
	37.91					
	12.00					
	14.82					

20 00		
—TABLE 2—(Continued)		
	LESS DILUTE NORMAL URINES	
	96 55	73 *
	25 50	72
		72

TABLE 2—(Continued)		LESS DILUTE NORMAL URINES		*NaHCO ₃ administered
350 00	446 55	96 55	73 *	
223 50	279 00	55 50	72 *	
188 16	250 08	61 92	72	
182 04	238 36	56 32	72	
172 00	244 40	72 40	71	
135 42	185 82	50 40	71	
8 80	34 00	25 20	61	
40 56	76 20	35 64	59	

[illegible]

40 56		CONTROL URINES		† Urine of same person as *
—TABLE 3—(Continued)				
188 50	231 34	42 84	72	
157 29	172 25	14 96	71	
75 80	115 00	39 20	67 †	
54 40	69 60	15 20	6 65	
66 40	93 20	26 80	6 65	

TABLE 3-

70280	8640
8750	6910

TABLE 4—URINES CONTAINING HEXAMETHYLLNAMIN—
VERY DILUTE URINES OF HOSPITAL PATIENTS

Acidity	Dosage gm	Dosage Times	Hexam Test	Uric Acid Content mg.	Total Uric Acid mg	Uric Acid Dissolved mg
74	10	4	+	4 66	22 50	17 84
695	10	4	+	5 07	46 98	41 91
675	10	4	+	6 53	68 47	61 94
675	06	4	Trace	4 66	77 28	72 62
67	10	4	+	5 49	48 65	43 16
665	06	4	+	4 66	54 46	49 80
645	10	4	+	4 24	44 91	40 67
645	06	4	+	5 08	31 80	26 72
64	10	4	+	4 85	42 22	37 37
64	06	4	+	6 32	37 86	31 54
635	10	4	+	4 20	39 40	35 20
635	06	4	+	4 20	39 00	34 80
635	10	4	+	3 80	20 20	16 40
635	10	4	+	4 20	18 20	14 00
635	06	4	+	4 20	17 80	13 60
63	10	4	+	4 60	43 00	38 40
63	06	4	+	4 66	35 37	30 71

DILUTE URINES OF HOSPITAL PATIENTS

TABLE 5—

715 *	06	5	+	10 44	189 52	179 08
715 *	10	4	+	4 25	105 92	101 67
70 *	10	4	+	13 79	117 54	103 75
69 *	10	4	+	10 05	103 01	92 96
685 *	06	4	+	10 98	119 71	108 73
685 *	10	4	+	15 03	83 09	68 06
68 *	06	4	+	11 81	84 85	73 04
675 *	06	5	+	16 36	80 74	64 38
675 *	06	4	+	10 98	62 44	51 46
65 *	06	5	+	13 40	69 64	56 24
645 *	06	5	+	11 92	74 82	62 90
64 *	06	3	+	10 15	67 42	57 27

LESS DILUTE URINES OF HOSPITAL PATIENTS

TABLE 6—

725 *	06	5	+	28 94	94 06	65 12
695 *	06	5	+	30 42	100 72	70 30
66 *	06	Every 2 hrs	+	82 58	86 51	3 93
635 *	06	Every 2 hrs	+	82 02	95 64	13 62
635 *	10	4	+	22 60	29 00	6 40
63 *	06	Every 2 hrs	+	95 64	99 45	3 81

—CONTROLS URINES CONTAINING NO HEXAMETHYLENAMIN

DILUTE URINES

Uric Acid Dissolved mg	Total Uric Acid mg	Uric Acid Content mg	Acidity	Remarks
144 75	154 50	9 75	7 3	The patients were typhoid cases Urines from typhoid patients when taking no drug
71 78	76 26	4 48	7 15	
105 66	122 16	16 50	6 95	
32 19	36 67	4 48	6 9	
41 07	45 55	4 48	6 85	
66 60	75 56	8 96	6 75	
37 74	42 59	4 85	6 75 +	
96 75	105 00	8 25	6 7	
48 00	56 40	8 40	6 7	
66 00	73 50	7 50	6 65	
61 60	72 40	10 80	6 45	
18 40	26 80	8 40	6 45	
46 95	74 90	27 95	6 4	
27 60	52 40	24 80	6 4	
22 94	30 42	7 48	6 35	
19 20	26 80	7 60	6 35	
13 60	21 20	7 60	6 35	
5 60	14 00	8 40	6 35	
33 75	41 25	7 50	6 3	
19 20	31 60	12 40	6 3	

—TABLE 5—(Continued)

DILUTE NORMAL URINES

144 75	154 50	9 75	7 3	* Case of pleurisy
157 29	172 25	14 96	7 1	* Case of typhoid fever
118 40	138 80	20 40	7 0	* Case of typhoid fever
141 75	150 08	8 33	6 9	* Case of typhoid fever
130 07	139 06	8 99	6 9	
136 16	144 50	8 34	6 85	* Case of pyelocystitis
109 29	128 69	19 40	6 85	* Case of typhoid fever
116 80	135 60	18 80	6 8	* Case of pyelocystitis
102 20	109 68	7 48	6 8	
83 00	91 25	8 25	6 75	* Case of pleurisy
66 60	75 56	8 96	6 75	* Case of pyelocystitis
50 80	66 00	15 20	6 5	* Case of pleurisy
49 58	59 28	9 70	6 5	
61 60	72 40	10 80	6 45	* Case of pleurisy
51 48	59 04	7 56	6 45	
48 75	68 40	19 65	6 4	* Case of septicemia

—TABLE 6—(Continued)

LESS DILUTE NORMAL URINES

188 50	234 34	45 84	7 2	* Case of pleurisy
182 04	238 36	56 32	7 2	
162 40	207 60	45 20	6 95	* Case of pleurisy
94 40	122 00	27 60	6 95	
96 79	123 60	26 81	6 6	* Case of typhoid fever
75 48	158 52	83 04	6 6	
29 36	107 96	78 60	6 35	* Case of typhoid fever
13 60	42 00	28 40	6 3	* Case of typhoid fever
10 20	78 60	68 40	6 3	* Case of typhoid fever
10 40	66 00	55 60	6 3	

uric acid dissolved by a control urine of this degree of acidity. This result is doubtless due to the fact that two doses were taken close together, amounting to almost the same thing as taking a single dose of 4 gm (compare the results reported in Table 7)

In Table 2 the high solvent power of the first urine must be compared (as is done in the table) with urines obtained after taking a similar dose of sodium bicarbonate as was taken with the drug. In both Tables 2 and 3 there is no evidence of solvent action due to hexamethylenamin

TABLE 7—CONTRAST OF TESTS WITH—
URINES OF NORMAL PERSONS AFTER AN EXCESSIVE DOSE OF HEXAMETHYLENAMIN

Acidity	Dosage gm	Time Hours	Hexam Test	Uric Acid Content mg	Total Uric Acid mg	Uric Acid Dissolved mg
64	40	0-1	++	69.84	265.92	196.08
60	40	0-2¼	++	44.00	262.88	218.88
60	40	0-4	++	61.48	209.68	148.20
58	40	0-2¼	+	72.12	79.72	7.60
57	40	0-2¼	++	9.80	49.32	39.52

In Tables 4, 5 and 6 only one urine (the first in Table 5, acidity 7.15) shows excess of uric acid dissolved (22 mg above the highest control reported). But it may well be that this urine should be compared with the less dilute controls, since its specific gravity was 1.010, and among these controls we find just as great solvent power (e.g., acidity 7.1—172 mg, acidity 7.0—187 mg and others)

In contrast with these findings the results given in Table 7 are quite striking. Four of the five persons taking the large dose of hexamethylenamin (equal to twenty-four hours medication for a patient) furnish urines which show greater solvent power than any controls of the same range of acidity. We have never found a normal urine of an acidity as great as 5.7 which has taken up *any* extra uric acid. Furthermore, the hexamethylenamin urines of acidity 6.0 and 6.4 dissolved as much uric acid as control urines of acidity 6.8 to 7.2. These urines with one previously considered (see comment on Table 1) make five urines which definitely show solvent action attributable in part to the drug, but in each of these cases the dosage was extra-therapeutic. We feel free to admit, therefore, that it is very probable that after administration of *excessive* doses of hexamethylenamin, certain portions of the urine secreted may contain a sufficient concentration of the drug

to impart to them a uric acid solvent action greater than those urines would otherwise manifest

This finding, however, is hardly of practical therapeutic application, first, because the required dose is too large, and second, because an equal effect can be secured more cheaply and easily by administration of alkaline diuretics or sodium bicarbonate in reasonable doses. For instance, if the urine be rendered faintly alkaline (7.1 to 7.4) by taking the latter agents, solvent action such as shown in Table 8 is readily obtained

—EXCESSIVE AMOUNTS AND WITH NO HEXAMETHYLENAMIN

CONTROLS URINES CONTAINING NO HEXAMETHYLENAMIN

Uric Acid Dissolved mg	Total Uric Acid mg	Uric Acid Content mg	Acidity	Remarks
48.75	68.40	19.65	6.4	
31.20	75.60	44.40	6.4	
37.92	52.33	14.41	6.0	
14.82	25.50	10.68	5.95	
40.56	76.20	35.64	5.9	
20.00	29.20	9.20	5.8	

The effect of artificially adding hexamethylenamin to normal urines was also studied and the comparison made of the amount of uric acid dissolved with that taken up by the untreated urine. In most cases the drug was added in such quantity as to give a concentration of 0.05 per cent, since this was considered the greatest amount that could occur in the urine following therapeutic dosage. The acidity of the urine was unaffected by the drug. The results are given in Table 9.

It is evident that the hexamethylenamin which was added has had little if any effect, since some of the urines show a few milligrams decrease and others a few milligrams increase, but in no case a marked increase even when 0.35 per cent of the drug is present.

As a final experiment, mixtures of monosodium and disodium phosphate solutions of concentrations similar to that of the phosphates in urines were tested as to their ability to take up uric acid both with and without added hexamethylenamin. These phosphate mixtures are quite similar to the normal urinary constituents which are most concerned in producing the hydrogen-ion concentration of urine. The results are as shown in Table 10.

TABLE 8—SOLVENT ACTION OF ALKALINE URINES

Acidity	Uric Acid Content	Total Uric Acid	Uric Acid Dissolved
7.3	96.55	446.55	350.00
7.3	105.00	360.75	255.75
7.3	70.50	283.87	213.37
7.3	129.24	313.85	184.61
7.25	56.00	227.20	171.20
7.25	72.00	222.26	150.26
7.2	55.50	279.00	223.50
7.2	52.02	218.94	166.92
7.15	27.00	210.41	183.41
7.1	30.57	197.88	167.31

TABLE 9—EFFECT OF ADDING HEXAMETHYLENAMINE TO NORMAL URINES

Acidity	Controls Uric Acid Dissolved (No Hexam.)	Uric Acid Dissolved (Hexam Added)	Hexam Per Cent
7.2	188.492	204.750	0.05
7.2	85.800	75.660	0.05
6.9	101.833	94.250	0.05
6.8	79.167	100.000	0.05
6.7	46.250	42.550	0.35
6.7	67.340	85.840	0.35
6.5	63.917	58.500	0.05
6.0	39.008	47.675	0.05

TABLE 10—SOLVENT ACTION OF PHOSPHATE SOLUTIONS

Acidity	Controls Phosphate Without Hexam Uric Acid Dissolved	Phosphate With Hexam Uric Acid Dissolved	Hexam Per Cent
7.15	154.00	155.60	0.05
6.8	102.00	105.20	0.05
6.25	26.80	28.00	0.05
7.15	154.00	147.60	0.1
6.8	102.00	108.40	0.1
6.25	26.80	31.60	0.1
6.8	61.20	81.20	1.0
6.65	38.80	74.00	1.0
6.45	32.40	62.00	1.0

The first two sections of the table show no dissolving power in excess of the controls, but the last section shows distinct and uniform solvent action attributable to the drug. Thus, as in the case of urine, we find that it is simply a question of the concentration of the hexamethylenamin, ordinary concentrations giving rise to no solvent action, but excessive concentrations causing solvent action.

Undoubtedly the reason why the stronger solutions show more distinct solvent action is because a greater amount of formaldehyd is set free than in weaker solutions, and it is the formaldehyd that causes solution of the uric acid. In neutral or slightly alkaline solutions formaldehyd is not set free from hexamethylenamin. Ordinary distilled water is sufficiently acid (due to CO_2) to induce the reaction. Hanzlik⁴ found no formaldehyd in urines of acidity 7.0 to 7.4 after administration of hexamethylenamin, but found it in almost every urine which was truly acid, 4.85 to 6.95. We found that a 1 per cent solution of the drug in a phosphate mixture of an acidity 7.2 dissolves a smaller amount of extra uric acid than does a 1 per cent solution in a phosphate mixture of the same concentration (1/30 gm molecular) but of greater acidity, 6.8.

TABLE 11—COMPARISON WITH EFFECT OF PHOSPHATE MIXTURE

Acidity	Control Phosphate Mixture Uric Acid Dissolved	Phosphate with Hexam Uric Acid Dissolved	Extra Uric Acid Dissolved	Hexam Per Cent
7.2	173.24	204.32	31.08	20
7.2	173.24	186.56	13.32	10
6.8	100.81	121.57	20.76	10

The question may be asked, why does the hexamethylenamin dissolve *any* extra uric acid in the alkaline mixture (7.2)? The answer is found in the fact that the acidity of the solution gradually changes as uric acid is taken up. The filtrate from the 7.2 control after shaking with uric acid had an acidity of 6.8. In consequence of this, formaldehyd was finally liberated in the hexamethylenamin phosphate solution (and dissolved extra uric acid), whereas in the more acid phosphate solution (6.8) formaldehyd was being liberated during the entire time of the shaking. It will be noticed in Table 11 that the 2 per cent solution has the greatest effect, the shorter time for liberation

⁴ Hanzlik, P. J., and Collins, R. J. THE ARCHIVES INT. MED., 1913, xii, 578

of formaldehyd (as compaired with the solution of acidity 68) being more than compensated for by the greater concentration of the drug

CONCLUSIONS

1 In the case of urines hexamethylenamin exerts a uric acid solvent action only after the administration of excessive doses

2 Alkaline diuretics impart to the urine as great solvent power as these excess doses of hexamethylenamin

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AN OXYDASE REACTION ON BLOOD SMEARS

A VALUABLE TEST IN THE IDENTIFICATION OF WHITE BLOOD CELLS OF UNCERTAIN ORIGIN¹

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In view of the uncertainty that exists as to the origin and status of many white cells of the blood and the difficulty in differentiating between some cells of myeloid and lymphoid origin such as the Naegeli myeloblast and the pathological lymphocyte, any procedure that affords additional information on this subject is of value. The demonstration of the content of any cell in oxydase ferments affords a biological reaction that is of great help, inasmuch as it has been shown that cells of myeloid origin contain such ferments and those of lymphoid origin do not. This difference was first definitely noted by Meyer¹ in 1903, who, following on the observation of Brandenburg² in 1900, that the blood in myeloid leukemia frequently gave a positive guaiac reaction without the presence of peroxid or turpentine, found that with this test granules of oxydase ferment could be demonstrated in the granulocyte cells of the blood but not in the lymphocytes. Later Winkler³ devised another and more reliable method based on the "indophenolblau" synthesis of Ehrlich⁴ (alpha-naphthol and dimethylparaphenyldiamin with one atom of oxygen form a white substance and with another blue "indophenolblau"), and demonstrated with this the oxydase granules in gonococcus pus and in leukocytes in the tissues, but not in lymphocytes⁵. This he suggested as a convenient method of proving inflammation in the appendix and other lymphoid tissue and predicted the coming usefulness of the test in the study

¹ Submitted for Publication Aug 25, 1915

² From The Clinical Laboratory of the Medical Clinic of The Johns Hopkins Hospital

1 Meyer, E. Beitrage zur Leukocytenfrage, Munchen med Wchschr, 1903, L-II, 1489

2 Brandenburg, K. Ueber die Reaktion der Leukocyten auf die Guaiaktinctur, Munchen med Wchschr, 1900, XLVII-1, 183

3 Winkler, F. Der Nachweis von Oxydase in den Leukozyten mittels der Dimethylparaphenyldiaminalphanaphtholreaktion, Folia Haemat, 1907, IV, 323

4 Ehrlich, P. Das Sauerstoffbedurfnis des Organismus, p 92, Berlin 1885, August Hirschwald

5 Winkler, F. Die Oxydasereaktion im gonorrhoeischen Eiter, Folia Haemat, 1908, V-VI, 17

of the origin of the different white blood cells. It is the reliability of this test and the possibilities that lie in its application to blood smears, and a technic for the same, that form the discussion in this paper.

Schultze⁶ submitted many body tissues to this "indophenolblau" reaction after formaldehyd fixation and found the oxydase granules in the tear and thyroid glands in addition to cells of myeloid origin. He, however, found these granules in no other body cells and used the test in the differential diagnosis of the leukemias. This work has been repeated by several others with similar results.⁷ Schultze later modified his technic⁸ by using sodium betanaphthol (Mikiozidine-Merck) and dimethylparaphenylendiamin hydrochlorid. With this the oxydase granules become a light green, and later, after treatment with water, a violet-black, and the fat droplets and lipid substances stain a reddish color that is to be distinguished from that of the oxydase granules. Gierke⁹ by the original "indophenolblau" synthesis brought the granules out in many body cells in fresh tissue but obtained results similar to those of Schultze after formaldehyd fixation and with an alkaline solution of the alphanaphthol which he used. To explain this phenomenon Gierke presents the hypothesis that the reaction on fresh tissue depends on the labile respiratory oxygenase, a peroxydase reaction, destroyed or inactivated by the formaldehyd fixation used by Schultze, whereas the more stabile oxydase of the myeloid cells endures. Kreibich¹⁰ speaks of the reaction in the myeloid cells also as a peroxydase reaction but believes it is specific for the myeloid cells. By treating the material with a 1 to 2 per cent solution of benzidin monosodium-sulphate to which 2 to 3 drops of 30 per cent perhydrol has been added, he claimed to obtain a preparation that demonstrated the peroxydases in only the granulocyte cells, and which resisted alcohol, xylol and balsam and might be counterstained with Loeffler's methylene blue, eosin or Ehrlich's stain. The "indophenolblau" oxydase reaction is of very short duration and counterstaining is difficult, so any such method as suggested by Kreibich for a permanent preparation that admits of staining is a great advantage. But so far his claims for the specificity of this peroxydase reaction have not been

6 Schultze, W. Zur Differentialdiagnose der Leukamien, München med. Wchnschr., 1909, Ivi, 167.

7 See Turk, W. Vorlesungen über Klinische Haematologie, p. 202, Wien und Leipzig, 1912, Wilhelm Braumüller.

8 Schultze, W. Weitere Mitteilungen über Oxydasereaktionen an Gewebsschnitten, München med. Wchnschr., 1910, Ivi-ii, 2171.

9 Gierke, E. Die Oxydierenden Zellfermente, München med. Wchnschr., 1911, Ivi-ii, 2315.

10 Kreibich, C. Ueber Oxydasen und Peroxydasen, Wien klin. Wchnschr., 1910, xxiii, 1443.

substantiated Klopfer¹¹ by the "indophenolblau" synthesis after formaldehyd fixation, found the oxydase granules only in the tear and thyroid glands and in the cells of myeloid origin, as did both Schultze and Gierke, and agreed with Gierke that the differentiation between a labile and stable ferment by formaldehyd fixation is sharp. Dietrich¹² maintained that the "indophenolblau" is a fat stain and that the oxidation is brought about by the general tissue metabolism, and then the fat droplets and lipid substances take up the stain. Gierke⁹ refuted this idea by showing that no granules appear after killing the ferments and adding the already oxidized solutions, and that granules still give the reaction after killing the cell life by chloroform but preserving the oxydases. However, the fat droplets in tissues are stained in the presence of the solutions used in the "indophenolblau" synthesis but they become a red-violet color, as noted by Schultze³ and Klopfer,¹¹ which is readily distinguished from the blue-black "indophenolblau" of the oxydase reaction. Recently Loele¹³ suggested the use of alpha-naphthol and gentian violet for the demonstration of these granules, whereby a permanent preparation may be obtained. But this, as he admits, is not an oxydase reaction and in common with the peroxydase method of Kriebich¹⁰ needs further study as to its specificity before it may be adopted as a reliable test.¹⁴

That the demonstration of the presence or absence of oxydase granules by the "indophenolblau" reaction after formaldehyd fixation is trustworthy in the differentiation of cells of myeloid and lymphoid origin seems well established. As such it is useful in making the diagnosis of the type of leukemia, and especially in that large cell variety of acute lymphatic leukemia which is so difficult on morphological and tinctorial grounds alone. The reaction is also of great help in the study of white blood cells of uncertain identity and in researches on cells whose origin is not yet established.

The test, therefore, seems to be of definite clinical and experimental value, and since no detailed method for blood smears is available in the literature, it was thought that the one here devised and found reliable and convenient in the study of many different white blood cell types might prove helpful.

11 Klopfer, A. Experimentelle Untersuchungen über die W. H. Schultze'sche Oxydasereaktion, *Ztschr. f. Exper. Path. u. Therap.*, 1912, 21, 467.

12 Dietrich, A. Naphtholblausynthese und Lipoidfärbung, *Centralbl. f. allg. Path. u. path. Anat.*, 1908, p. 3.

13 Loele, W. Bemerkungen zur Oxydasereaktion, *Folia Haemat.*, 1914, XVIII, 581.

14 For discussion of the various modifications of the indophenolblau oxydase reaction see Nakano, J. Beiträge zur Kenntnis der histologischen Oxydaseraktion der Supravital- und Vitalfärbung, *Folia Haemat.*, 1913, XV, 123.

TECHNIC FOR BLOOD SMEARS

The technic on blood smears is necessarily somewhat more exact than on smears of pus and on tissue sections. The reliable identification of the cells containing oxydase granules demands that the smear be preserved by satisfactory fixation and that some method of counterstaining be available whereby the different nuclei may be recognized. In any technic the labile character of the ferment granules and the short duration of the "indophenolblau" reaction is to be considered. The methods suggested by Kreibich,¹⁰ Loele¹² and others¹⁴ for obtaining permanent preparations that demonstrate a difference in ferment content of the lymphoid and myeloid cells, have not yet been proved sufficiently reliable to admit of general adoption. The age of the smear is of importance too, for although tissue sections are said to give the reaction when a year old,⁷ blood smears in this laboratory failed to give the usual reaction when over six weeks old. Fresh smears should be used whenever possible.

A Fixation—The usual fixing methods employed kill the ferments and are therefore forbidden. Alcohol is said not to injure the oxydases and is advised by some, but in this laboratory immersion for five minutes in absolute methyl or ethyl alcohol failed to give reliable fixation without injuring the ferments, and furthermore, that the test be specific as shown by Gierke⁸ and Klopfer.¹¹ Formaldehyd solution must be used in some form. Immersion for short periods in Formol-Muller solution or in 40 per cent solution of formaldehyd and exposure to formaldehyd vapor has been used successfully on tissue sections. On blood smears, however, Formol-Muller solution and formaldehyd solution in various strengths were found to be mutilating and were therefore discarded. Formaldehyd vapor was entirely satisfactory, and using a 10 per cent solution of the formalin (40 per cent formaldehyd gas), an exposure to this in a closed jar for six to eight hours fixed all smears and injured none, although three hours fixed some and twenty-four hours did not injure others. An exposure to stronger solutions for shorter periods is not advisable, but a 25 per cent solution for one to two and one-half hours may be used. The vapor of undiluted formaldehyd fixes the smears in a closed jar in ten minutes but weakens the oxydase reaction in such a way that, although most polymorphonuclear cells still show the granules, many myeloblasts, myelocytes, and so-called transitional cells do not.

B Staining—In staining, aqueous solutions used without a mordant are necessary for the stains also must be of such composition that the ferments are not injured by them. The Romanowski stains and Ehrlich stain are forbidden by reason of the alcohol and heat, respectively, used in the technic. The blue nuclear stains do not give sharp differentiation. Aqueous gentian-violet and Giemsa stain are washed out by the aqueous solution of alpha-naphthol and dimethylparaphenyldiamin used in the subsequent "indophenolblau" synthesis too rapidly to be of any value. Saturated aqueous vesuvium and the vesuvium synthesis of Unna by means of metadiamin and sodium nitrite, suggested by Winkler⁵ for differentiating nuclei and bacteria in smears of pus, stained the nuclei too faintly to be useful for blood smears. All the red nuclear stains were tried in aqueous solution and lithium carmine as used by Gierke⁸ on tissue sections. Of these, only saturated aqueous safranin and 2 per cent aqueous pyronin gave the desired intensity of staining in a short time. With either of these solutions the fixed smear is covered for eight minutes, is washed quickly and dried immediately by careful blotting. By this method the red cells and other elements remain unstained and the nuclei become an intense orange-pink that readily admits of the identification of the cell.

The staining must be done before the oxydase reaction for, if the oxydase reaction is done first, during the eight minutes consumed in staining the nuclei the "indophenolblau" has in large part faded out of many of the granules. In

some instances, when the cell type under investigation in regard to its oxydase content predominates in the smear and is readily recognized, as in the acute leukemias, the stain may be omitted

C The Oxydase Reaction—Solutions 1 One per cent aqueous solution of dimethylparaphenyldiamin This is a translucent, dark-purple solution when freshly made up, but later gets cloudy It is supposed to be efficacious for only eight to fourteen days,⁷ but here it was found to react well at the end of three weeks

2 One per cent aqueous solution of alphanaphthol dissolved by gentle heating, or preferably, 1 per cent solution of alphanaphthol in 1 per cent KOH In this alkaline solution very little heating is necessary to bring about complete solution of the alphanaphthol When fresh this should be a clear solution with a very faint brownish tinge It rapidly becomes a deeper brown and is of no value at the end of the fourth day

Procedure Put one drop of Solution 1 and one drop of Solution 2 on a slide (a dirty, milky fluid resulting) and mount the smear, fixed, or fixed and stained according to the technic above outlined, in this and examine at once Immediate examination is essential, for the nuclear stain endures only a few minutes in such intensity that definite identification of the cells may be made If possible, before the oxydase reaction has become complete, locate a cell that is to be tested for oxydase granules At first there is a very faint, diffuse blue of the protoplasm Then small granules and finally many coarse blue-black granules appear, usually confined entirely to the protoplasm but occasionally seen to overlie the nucleus The granules in the mature cells are frequently coarser than those in the immature ones The height of the reaction is reached in about two minutes and endures about ten minutes Another convenient procedure is to mount the stained smear on a slide film side upward and examine with the low or high dry objective till a field containing cells to be tested is located The slide is then clamped down and the solutions added directly on the cover slip With the low power objective the progress of the oxydase reaction in the cells may be watched and when it has reached its height (in about two minutes) the cover slip is carefully blotted and the field can then be examined with the high dry objective Dry and in the air the oxydase reaction endures in its original intensity for from twenty to thirty minutes

No satisfactory medium for mounting the preparation has as yet been found¹⁴ Xylol, balsam, and cedar oil quickly destroy the "indophenolblau" oxydase reaction Winkler⁶ used a solution of benzol and colophonium in equal parts for tissue sections and smears of pus, but this did not prove satisfactory for blood smears

SUMMARY

1 Use blood smears as fresh as possible, and certainly not more than six weeks old

2 Fix six to eight hours in the vapor of 4 per cent formaldehyd solution in a closed jar

3 Stain eight minutes in a saturated aqueous safranin or a 2 per cent aqueous pyronin solution, wash, and dry immediately

4 Examine the smear and become familiar with the appearance of the various cell types with the nuclei thus stained

5 (a) Put one drop of Solution 1 (less than three weeks old) and one drop of Solution 2 (less than four days old) on a slide, mount the smear in this and examine at once, or

(b) Mount the smear film side upward on a slide and put Solutions 1 and 2 directly on the smear, watch the reaction with the low power objective progress to its height, and at the end of two minutes dry and examine with the high dry objective

The above procedure has been found a convenient and reliable method on blood smears for demonstrating the presence or absence of oxydase granules in many varieties of white blood cells, and by reason of the differentiation between cells of myeloid and lymphoid origin made possible, gives a preparation that is of great value in determining the status and origin of white blood cells of uncertain identity

BOOK REVIEW

INFECTION, IMMUNITY AND SPECIFIC THERAPY By John A. Kolmer, M.D.,
Dr. P. H., Instructor of Experimental Pathology, University of Pennsylvania

This pretentious volume of 900 pages consists of (1) a comprehensive review of the theory of infection and immunity, (2) detailed descriptions of serological tests and the methods of vaccine and serum therapy.

The author has gone to great pains to be explicit in describing laboratory methods, and in this respect the book will be a valuable addition to the comparatively small number of laboratory manuals which have been written in English.

The technic of performing the various biological tests is given step by step, in such a way that any one trained in serological work can readily perform them. Complement fixation methods, for example, are described at length, not only for syphilis and gonorrhea, but for other infections. Vaccine therapy (including tuberculin) receives only twenty-five pages, which appears rather meager in a treatise of this kind. The book contains many illustrations, most of which serve to demonstrate some point in technic.

Dr. Kolmer's style is simple and lucid and there are very few inaccuracies, the most noticeable is the statement that a positive Wassermann rarely appears before the seventh or eighth week after a syphilitic infection.

In the discussion of tests preliminary to transfusion, there should also be some reference to the isoagglutinin and isohemolysin groups which have been studied by Moss, Ottenberg and others.

Dr. Kolmer's book is a valuable contribution to the subject and will no doubt meet with considerable popularity, especially among laboratory workers.

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As a test of motility in those cases in which the stomach tube is contraindicated or refused, Bassler²⁷ uses a mixed-meal method by which he gives 25 gm of bismuth subcarbonate with the Riegel meal and examines by the Roentgen ray six hours later, at which time the stomach should be empty. In marked pyloric stenosis he has noted a residue at twelve hours, or much later, even to five days. However, in a subsequent publication, Bassler²⁸ has this to say

In the study of motility and exit from the stomach in 203 cases of distinct gastroparesis, in which hourly Roentgen ray observations were made, the conclusion was plain that the Roentgen ray method of diagnosing stasis in the stomach is not as practical as the test-meal method. One hundred and twenty-six of these cases examined by the bismuth-Roentgen-ray method showed delay of exit of six hours or more, while only thirty-one showed the delay by the test-meal method.

Instances were encountered in which bismuth was present in the stomach as late as eighteen hours after ingestion, while the stomach on a mixed meal was empty in four and one-half hours.

It is apparent, whatever has been advanced to the contrary, that the method of examination by food extraction is decidedly more to be depended on in gaining an idea of exit from the stomach than is the bismuth Roentgen ray method, for it was strongly suggested that foods pass from the stomach in decidedly less time than will bismuth or any other form of metal salts used to throw a shadow, probably because of the pulverized salts adhering to the mucosa.

The most faithful advocate of the Roentgen motility test is Haudek,²⁹ and to him we are indebted for the double-meal method of examination, the establishment of the six-hour limit and a vast deal of information concerning the significance of disordered motility as shown by the Roentgen ray. The rather chaotic application of the Roentgen examination for motility led Haudek, in 1909, to establish his double-meal method, partly with the view of saving time and partly to make the test more precise. Accordingly, he began the administration of a Rieder meal in the morning, and examined the patient six hours later, at which time a second Rieder meal was given to complete the examination. The selection by Haudek of six hours as the division line between normal and delayed emptying was explained by him on the ground that while the normal stomach will drive out a Rieder meal in about three hours, as an average, delay to five or six hours might result from physiologic causes. He cited as examples the influence of rest and movement, right and left-side positions, psychic factors, eating or drinking after taking the meal, and sedimentation of the opaque salt

27 Bassler. *Diseases of the Stomach and Upper Alimentary Tract*. Philadelphia, F. A. Davis Company, 1913, p. 213.

28 Bassler, A. Some Recent Conclusions on Abdominal Roentgen Ray Work, *Jour. Am. Med. Assn.*, 1913, lxi, 2217.

29 Haudek, M. Die Technik und Bedeutung der Radiologischen Motilitätsprüfung, *Verhandl. d. 31. Deutsch. Kongr. f. inn. Med.*, J. F. Bergmann, Wiesbaden, 1912, p. 143.

Even after six hours or longer minute residues might sometimes be found in normal stomachs, and he accordingly ignored mere traces. Small residues, up to a quarter of the meal, he deemed, could be due not only to organic pathologic changes but also to hypomotility from atony, hyperacidity, or long *hubhohe*, that is, a long, vertical pars pylorica. Larger residues could be almost certainly ascribed to pyloric obstruction by organic stenosis or spasm from ulcer. He also pointed out that the test did not rest alone on the presence or absence of a residue, but that the position of the "head" of the six-hour meal gave gross information as to motility. Normally at or near the cecum, the "head" would be advanced far into the large intestine by hypermotility or held back in the small intestine by hypomotility. Further, on giving the second meal, there could also be taken into consideration the tonus of the stomach, its peristalsis, the freedom of passage through the pylorus, the *hubhohe*, and thus the total picture would enable an estimation of "the great X of motility, the functioning of the pylorus."

An experience of years with thousands of cases has increased Haudek's confidence in the method. In a recent article, he³⁰ goes so far as to say that the Roentgen determination of the expelling forces of the stomach gives better results than the older methods, and that it is not only exact and reliable but also very simple. He shows that while the clinical examination cannot determine whether the increase or decrease of motility is due to a change of the expelling power or of the resistance, the Roentgen examination can be much more decisive. While he had previously considered atony to be an occasional cause of six-hour retention he now believes that atony, under otherwise normal conditions, causes only a slight increase of evacuation time, usually below six hours. The most important factor for the evacuation of the stomach is the condition of the pylorus. Lessening of resistance produces the picture of pyloric insufficiency, an increase leads to the highest degrees of stagnation. He enumerates the common causes of increased resistance, both organic and spastic, and cites examples as varied by the functional components of motility. He also mentions Sahli's method of testing the motility with sinking and swimming capsules in differentiating between pylorospasm and organic stenosis, also the effect of papaverin in these conditions. By means of Sahli's capsules the evacuation time of water can be shown, this is usually normal in pylorospasm but prolonged in stenosis. According to Holzknecht the administration of papaverin shortens the emptying time in pylorospasm to normal, increases it in stenosis, and has no effect on a combination of the two.

30 Haudek, M. Ueber die Radiologische Prüfung der Magenmotilität und Ihre Resultate, *Fortschr. a. d. Geb. d. Roentgenstrahlen*, 1914, **XXI**, 472.